EFFICACY AND TOLERABILITY OF VITAMIN C AS AN ADD ON THERAPY TO THE STANDARD ANTI HYPERTENSIVE REGIMEN IN THE REDUCTION OF BLOOD PRESSURE AND C REACTIVE PROTEIN LEVELS IN HYPERTENSIVE PATIENTS

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CERTIFICATE

This is to certify that the dissertation entitled, **"Efficacy and tolerability of Vitamin C as an add-on therapy to standard anti-hypertensive regimen in the reduction of blood pressure and C reactive protein levels in hypertensive patients"** submitted by **Dr.S.Gunasakaran,** in partial fulfillment for the award of the degree of Doctor of Medicine in Pharmacology by The Tamilnadu Dr.M.G.R. Medical University, Chennai is a bonafide record of the work done by him in the Institute of Pharmacology, Madras Medical College, during the academic year 2005 – 2008.

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DEDICATION

I dedicate this book to my Dad **Late Mr. A. Sambandan** who wanted me to be an aspiring Doctor.

“Miss u Dad”

Last but not the least, I sincerely thank my **Mother** and **Brother** for their continuous encouragement, patience, valuable support and sincere prayers without which I could not have completed this work successfully.

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INTRODUCTION

An elevated arterial blood pressure is probably the most important public health problem in both developing and developed countries. It is common, mostly asymptomatic, readily detectable, usually easily treatable, and often leads to lethal complications if left untreated.[1]

The prevalence of hypertension in white suburban population according to the Framingham study is nearly one fifth of individuals have blood pressures > 160/95 mm Hg, while almost one half have pressures > 140/90 mm Hg. In females the prevalence is closely related to age, with a substantial increase occurring after the age of 50. This increase is presumably related to the hormonal changes of menopause. Thus, the ratio of hypertension frequency in women versus men increases from 0.6 to 0.7 at age of 30 to 1.1 to 1.2 at the age of 65. [1]

Cardiovascular diseases caused 2.3 million deaths in India in the year 2005 and this is projected to double by the year 2020. Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary artery disease deaths in India. In India, it has been found that hypertension prevalence is 24% among men and 17% among women in the year 2007.[2]

Hypertension is considered to be present when a person's systolic blood pressure is consistently 140 mm Hg or greater, and / or their diastolic blood pressure is consistently 90 mm Hg or greater. Recently, The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood pressure has defined blood pressure 120 / 80 mm Hg to 139/89 mm Hg as Pre-hypertension. Pre-hypertension is not a

disease category; rather, it is a designation chosen to identify individuals at high risk of developing hypertension.[3]

Untreated hypertension will lead to various complications. Complications due to hypertension are related either to sustained elevations of blood pressure, with consequent changes in the vasculature and heart, or to atherosclerosis that accompanies and is accelerated by long standing hypertension. Cardiac complications are the major causes of morbidity and mortality in hypertension and preventing them is a major goal of therapy. Cardiac complications of hypertension includes left ventricular hypertrophy, left ventricular dysfunction, congestive cardiac failure, ventricular arrhythmias, myocardial infarction and sudden death.[4] The other complications of hypertension includes occurrence of stroke, especially intracerebral hemorrhage and ischemic cerebral infarction, hypertensive retinopathy, hypertensive nephropathy, aortic dissection and so on.

There are now many classes of potentially available anti-hypertensive drugs of which five (ACE inhibitors, diuretics, beta blockers, calcium channel blockers and angiotension receptor blockers(ARBs) are suitable for single drug therapy based on efficacy and tolerability. The first line of drug therapy of choice for the treatment of hypertension is ACE inhibitors. [5]

The involvement of inflammation and its mediators in hypertension, cardiovascular pathophysiology and atherogenesis is increasingly recognized[6]. Plasma level of inflammatory molecules such as C-reactive protein (CRP); cytokines, such as tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6); chemokines, such as monocyte chemoattractant protein (MCP-1) and adhesion molecules, such as P-selectin[7] and leucocyte adhesion

molecules, intercellular adhesion molecules (ICAM-1), are increased in patients with essential hypertension and increased CRP level[8] has also been reported to be a predictor of future cardiovascular disease such as incidence of coronary artery disease, myocardial infarction and cerebrovascular accidents such as stroke.[9]

None of the standard anti-hypertensive drugs has been found to be effective in reducing the levels of C-reactive protein which is a better predictor of future cardiovascular and cerebrovascular complications.

Vitamin C, one of the water soluble vitamin, being a strong reducing agent, provides protection to various organs against oxidizing agents, and reduces oxidation of low density lipoproteins and prevents deposition of atheromatous plaques and incidence of stroke. It helps in maintenance of vascular integrity through prostacyclin, antiplatelet and vasodilatory effects. Vitamin C improves endothelial dependent vasodilatation by improving nitric oxide activity in hypertensive patients.[10]

Several animal studies[11] and clinical trials suggest that Vitamin C reduces C-reactive protein levels[12] in addition to the reduction of blood pressure[13] and oxidized LDL cholesterol levels. Hence this open-label prospective, randomized, parallel group study is undertaken to find out the efficacy and tolerability of vitamin C as an add on therapy to standard anti hypertensive regimen in the reduction of C-reactive protein and blood pressure.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Hypertension, commonly referred to as "high blood pressure", is a medical condition in which the blood pressure is chronically elevated. Hypertension can be classified as either

1. Primary Hypertension
2. Secondary Hypertension

Primary hypertension indicates that no specific medical cause can be found to explain a patient's condition. Secondary hypertension indicates that the high blood pressure is a result of (i.e. secondary to) another condition, such as kidney disease or certain tumors (especially of the adrenal gland). Persistent hypertension is one of the risk factors for strokes, heart attacks, heart failure and arterial aneurysm, and is a leading cause of chronic renal failure. Even moderate elevation of arterial blood pressure leads to shortened life expectancy. At severely high pressures, mean arterial pressures 50% or more above average, a person can expect to live not more than a few years unless appropriately treated.[14]

Salt sensitivity

Sodium is the environmental factor that has received the greatest attention. It is to be noted that approximately 60% of the essential hypertension population is responsive to sodium intake. This is due to the fact that increasing amounts of salt in a person's bloodstream causes the body to draw more water, increasing the pressure on the blood vessel walls.[15]

Role of renin

Renin is a hormone secreted by the juxtaglomerular cells of the kidney and linked with aldosterone in a negative feedback loop. The range of renin

activity observed in hypertensive subjects tends to be broader than in normotensive individuals. In consequence, some hypertensive patients have been defined as having low-renin and others as having essential hypertension.

Low-renin hypertension is more common in African Americans than Caucasians and may explain why they tend to respond better to diuretic therapy than drugs that interfere with the renin-angiotensin system.

High Renin levels predispose to hypertension: Increased renin --> Increased angiotensin II --> Increased vasoconstriction, thirst/ADH and aldosterone --> Increased sodium re-absorption in the kidneys (DCT and CD) --> Increased blood pressure.[16]

Genetics

Hypertension is one of the most common complex disorders, with genetic heritability averaging 30%. Data supporting this view emerge from animal studies as well as in population studies in humans. Most of these studies support the concept that the inheritance is probably multifactorial or that a number of different genetic defects each have an elevated blood pressure as one of their phenotypic expressions.[17]

More than 50 genes have been examined in association studies with hypertension, and the number is constantly growing.[18]

Etiology of secondary hypertension

Only in a small minority of patients with elevated arterial pressure, can a specific cause be identified. These individuals will probably have an endocrine or renal defect that, if corrected, could bring blood pressure back to normal values.

Renal hypertension

Hypertension produced by diseases of the kidney. This includes diseases such as polycystic kidney disease or glomerulonephritis.[16] Hypertension can also be produced by diseases of the renal arteries supplying the kidney. This is known as renovascular hypertension; it is thought that decreased perfusion of renal tissue due to stenosis of a main or branch renal artery activates the renin-angiotensin system.

Adrenal hypertension

Hypertension is a feature of a variety of adrenal cortical abnormalities. In primary aldosteronism there is a clear relationship between the aldosterone-induced sodium retention and the hypertension.

In patients with pheochromocytoma increased secretion of catecholamines such as epinephrine and norepinephrine by a tumor (most often located in the adrenal medulla) causes excessive stimulation of adrenergic receptors, which results in peripheral vasoconstriction and cardiac stimulation. This diagnosis is confirmed by demonstrating increased urinary excretion of epinephrine and norepinephrine and/or their metabolites (vanillylmandelic acid).

Hypercalcemia, Coarctation of aorta are other secondary causes of hypertension.

Pathophysiology

Most of the secondary mechanisms associated with hypertension are generally fully understood, and are outlined at secondary hypertension. However, those associated with essential (primary) hypertension are far less understood. What is known is that cardiac output is raised early in the disease

course, with total peripheral resistance (TPR) normal; over the time cardiac output drops to normal levels but TPR is increased. Three theories have been proposed to explain this:

Theory 1 :

Inability of the kidneys to excrete sodium, resulting in natriuretic factors such as Atrial Natriuretic Factor being secreted to promote salt excretion with the side-effect of raising total peripheral resistance.[19]

Theory 2 :

An overactive renin-angiotension system leads to vasoconstriction and retention of sodium and water. The increase in blood volume leads to hypertension.[20]

Theory 3 :

An overactive sympathetic nervous system, leading to increased stress responses.[21]

It is also known that hypertension is highly heritable and polygenic (caused by more than one gene) and a few candidate genes have been postulated in the etiology of this condition.[18,19,20]

Signs and symptoms :

Hypertension is usually found incidentally - "case finding" - by healthcare professionals during a routine checkup. The only test for hypertension is a blood pressure measurement. Hypertension in isolation usually produces no symptoms although some people report headaches, fatigue, dizziness, blurred vision, facial flushing or tinnitus.[20,21] Malignant hypertension (or accelerated hypertension) is distinct as a late phase in the

condition, and may present with headaches, blurred vision and end-organ damage.

It is recognized that stressful situations can increase the blood pressure.

Hypertension is often confused with mental tension, stress and anxiety. While chronic anxiety is associated with poor outcomes in people with hypertension, it alone does not cause it. Accelerated hypertension is associated with somnolence, confusion, visual disturbances, nausea and vomiting (hypertensive encephalopathy).[22]

Complications

While elevated blood pressure alone is not an illness, it often requires treatment due to its short- and long-term effects on many organs. The risk is increased for:

1. Cerebrovascular accident (CVAs or strokes)
2. Myocardial infarction (heart attack)
3. Left ventricular dysfunction
4. Cardiac arrhythmias
5. Hypertensive cardiomyopathy (heart failure due to chronically high blood pressure)
6. Hypertensive retinopathy - damage to the retina
7. Hypertensive nephropathy - chronic renal failure due to chronically high blood pressure

Pregnancy

Although few women of childbearing age have high blood pressure, up to 10% develop hypertension of pregnancy. While generally benign, it may herald three complications of pregnancy: pre-eclampsia, HELLP syndrome

and eclampsia. Follow-up and control with medication is therefore often necessary.

Hypertension in Children and Adolescents

As with adults, blood pressure is a variable parameter in children. It varies between individuals and within individuals from day to day and at various times of the day. The epidemic of childhood obesity, the risk of developing left ventricular hypertrophy, and evidence of the early development of atherosclerosis in children would make the detection of and intervention in childhood hypertension important to reduce long-term health risks; however, supporting data are lacking.

Most childhood hypertension, particularly in preadolescents, is secondary to an underlying disorder. Renal parenchymal disease is the most common (60 to 70%) cause of hypertension. Adolescents usually have primary or essential hypertension, making up 85 to 95 % of cases. [23]

GRADING OF HYPERTENSION :[24]

Sl. No	**Category**	**Systolic BP (mm Hg)**	**Diastolic BP (mm Hg)**
1	Normal	< 130	<85
2	High normal	130 – 139	85 – 90
3	Mild hypertension	140 – 159	90 -99
4	Moderate hypertension	160 -179	100 -109
5	Severe hypertension	> 180	> 110

ACE INHIBITORS :

ACE inhibitors decreases blood pressure by inhibiting the conversion of Angiotensin I to Angiotension II, which increases the sodium and water retention, Increases the aldosterone secretion thereby raises the blood pressure.

Enalapril

Enalapril maleate, the second ACE inhibitor approved in the United States, is a prodrug hydrolyzed by esterases in the liver to produce the active decarboxylic acid, enalaprilat. Enalaprilat is a highly potent inhibitor of ACE. Although it also contains a “praline surrogate”, enalaprilat differs from Captopril in that it is an analogue of a tripeptide rather than of a dipeptide.

Pharmacokinetics :

Enalapril is absorbed rapidly when given orally and has an oral bioavailability of about 60% (not reduced by food). Although peak concentrations of enalapril in plasma occur within an hour, enalaprilat concentrations peak only after 3 to 4 hours. Enalapril has a half-life of only 1.3 hours, but enalaprilat, because of tight binding to ACE, has a plasma half-life of about 11 hours. Nearly all the drug is eliminated by kidneys as either intact enalapril or enalaprilat. [25]

The oral dosage of enalapril ranges from 2.5 mg to 40 mg daily (Single or Divided doses), with 2.5 mg and 5 mg daily being appropriate for the initiation of therapy for heart failure and hypertension, respectively.

VITAMIN C

Vitamin C or L-ascorbate is an essential nutrient for higher primates, and a small number of other species. The presence of ascorbate is required for a range of essential metabolic reactions in all animals and plants and is produced internally by almost all organisms, humans being one notable exception. It is widely known as the vitamin whose deficiency causes scurvy in humans. It is also widely used as a food additive.

The pharmacophore of vitamin C is the ascorbate ion. In living organisms, ascorbate is an antioxidant, as it protects the body against oxidative stress[26], and is a cofactor in several vital enzymatic reactions.

Biological significance

Vitamin C is purely the L-enantiomer of ascorbate; the opposite D-enantiomer has no physiological significance. Both forms are mirror images of the same molecular structure. When L-ascorbate, which is a strong reducing agent, carries out its reducing function, it is converted to its oxidized form, L-dehydroascorbate. L-dehydroascorbate can then be reduced back to the active L-ascorbate form in the body by enzymes and glutathione.

L-ascorbate is a weak sugar acid structurally related to glucose which naturally occurs either attached to a hydrogen ion, forming ascorbic acid, or to a metal ion, forming a mineral ascorbate.

Functions

In humans, vitamin C is a highly effective antioxidant, acting to lessen oxidative stress, a substrate for ascorbate peroxidase, as well as an enzyme

cofactor for the biosynthesis of many important biochemicals. Vitamin C acts as an electron donor for eight different enzymes.

These enzymes participate in collagen hydroxylation.[27] These reactions add hydroxyl groups to the amino acids proline or lysine in the collagen molecule (via prolyl hydroxylase and lysyl hydroxylase), thereby allowing the collagen molecule to assume its triple helix structure and making vitamin C essential to the development and maintenance of scar tissue, blood vessels, and cartilage.[28]

These enzymes are necessary for synthesis of carnitine.[29] Carnitine is essential for the transport of fatty acids into mitochondria for ATP generation.

Deficiency

Scurvy is an avitaminosis resulting from lack of vitamin C, as without this vitamin, the synthesised collagen is too unstable to meet its function. Scurvy leads to the formation of liver spots on the skin, spongy gums, and bleeding from all mucous membranes.

The spots are most abundant on the thighs and legs, and a person with the ailment looks pale, feels depressed, and is partially immobilized. In advanced scurvy there are open, suppurating wounds and loss of teeth and, eventually, death. The human body cannot store vitamin C, and so the body soon depletes itself if fresh supplies are not consumed through the digestive system.

History of human understanding of Vitamin C

James Lind, a British Royal Navy surgeon in 1747, identified that a quality in fruit prevented the disease of scurvy in what was the first recorded controlled experiment.

The need to include fresh plant food or raw animal flesh in the diet to prevent disease was known from ancient times. Native people living in marginal areas incorporated this into their medicinal lore. For example, spruce needles were used in temperate zones in infusions, or the leaves from species of drought-resistant trees in desert areas.

In 1536, the French explorer Jacques Cartier, exploring the St. Lawrence River, used the local natives' knowledge to save his men who were dying of scurvy. He boiled the needles of the arbor vitae tree to make a tea that was later shown to contain 50 mg of vitamin C per 100 grams.

Throughout history, the benefit of plant food to survive long sea voyages has been occasionally recommended by authorities. John Woodall, the first appointed surgeon to the British East India Company, recommended the preventive and curative use of lemon juice in his book "The Surgeon's Mate", in 1617. The Dutch writer, Johann Bachstrom, in 1734, gave the firm opinion that "scurvy is solely owing to a total abstinence from fresh vegetable food, and greens; which alone is the primary cause of the disease."

While the earliest documented case of scurvy was described by Hippocrates around the year 400 BC, the first attempt to give scientific basis for the cause of this disease was by a ship's surgeon in the British Royal Navy, James Lind. Scurvy was common among those with poor access to fresh fruit and vegetables, such as remote, isolated sailors and soldiers.

While at sea in May 1747, Lind provided some crew members with two oranges and one lemon per day, in addition to normal rations, while others continued on cider, vinegar, sulfuric acid or seawater, along with their normal rations. In the history of science this is considered to be the first occurrence of

a controlled experiment comparing results on two populations of a factor applied to one group only with all other factors the same. The results conclusively showed that citrus fruits prevented the disease. Lind published his work in 1753 in his Treatise on the Scurvy.

Lind's work was slow to be noticed, partly because he gave conflicting evidence within the book, and partly because the British admiralty saw care for the well-being of crews as a sign of weakness. In addition, fresh fruit was very expensive to keep on board, whereas boiling it down to juice allowed easy storage but destroyed the vitamin (especially if boiled in copper kettles). Ship captains assumed wrongly that Lind's suggestions didn't work because those juices failed to cure scurvy.

It was 1795 before the British navy adopted lemons or lime as standard issue at sea. Limes were more popular as they could be found in British West Indian Colonies, unlike lemons which weren't found in British Dominions, and were therefore more expensive. This practice led to the American use of the nickname "limey" to refer to the British. Captain James Cook had previously demonstrated and proven the principle of the advantages of fresh and preserved foods, such as sauerkraut, by taking his crews to the Hawaiian Islands and beyond without losing any of his men to scurvy. For this otherwise unheard of feat, the British Admiralty awarded him a medal.

The name "antiscorbutic" was used in the eighteenth and nineteenth centuries as general term for those foods known to prevent scurvy, even though there was no understanding of the reason for this. These foods included but were not limited to: lemons, limes, and oranges; sauerkraut, cabbage, malt, and portable soup.

In 1907, Axel Holst and Theodor Frolich, two Norwegian physicians studying beriberi contracted aboard ship's crews in the Norwegian Fishing Fleet, wanted a small test mammal to substitute for the pigeons they used. They fed guinea pigs their test diet, which had earlier produced beriberi in their pigeons, and were surprised when scurvy resulted instead. Until that time scurvy had not been observed in any organism apart from humans, and had been considered an exclusively human disease.

Discovery of Vitamin C

In 1912, the Polish-American biochemist Casimir Funk, while researching deficiency diseases, developed the concept of vitamins to refer to the nutrients which are essential to health. Then, from 1928 to 1933, the Hungarian research team of Joseph L Svirbely and Albert Szent-Gyorgyi and, independently, the American Charles Glen King, first isolated vitamin C and showed it to be ascorbic acid. For this, Szent-Gyorgyi was awarded the 1937 Nobel Prize in Medicine.

Therapeutic uses

Since its discovery vitamin C has been considered by some enthusiastic proponents a "universal panacea", although this led to suspicions by others of it being over-hyped. Other proponents of high dose vitamin C consider that if it is given "in the right form, with the proper technique, in frequent enough doses, in high enough doses, along with certain additional agents and for a long enough period of time, it can prevent and, in many cases, cure, a wide range of common and/or lethal diseases, notably the common cold, hypertension and heart disease, Some proponents issued

controversial statements involving it being a cure for AIDS, bird flu, and SARS.[30]

Probably the most controversial issue, the putative role of ascorbate in the management of AIDS, is still unresolved for more than 16 years after the landmark study published in the Proceedings of National Academy of Sciences (USA) showing that non toxic doses of ascorbate suppress HIV replication in vitro.[31] Other studies expanded on those results, but still, no large scale trials have yet been conducted.[32]

In an animal model of lead intoxication, vitamin C demonstrated "protective effects" on lead-induced nerve and muscle abnormalities.[33] In smokers, blood lead levels declined by an average of 81% when supplemented with 1000 mg of vitamin C, while 200 mg were ineffective, suggesting that vitamin C supplements may be an "economical and convenient" approach to reduce lead levels in the blood.[34] The Journal of the American Medical Association published a study which concluded, based on an analysis of blood lead levels in the subjects of the Third National Health and Nutrition Examination Survey, that the independent, inverse relationship between lead levels and vitamin C in the blood, if causal, would "have public health implications for control of lead toxicity".

Vitamin C has limited popularity as a treatment for autism spectrum symptoms. A 1993 study of 18 children with Autism Spectrum Disorder (ASD) found some symptoms reduced after treatment with vitamin C, but these results have not been replicated. Small clinical trials have found that vitamin C might improve the sperm count, sperm motility, and sperm morphology in infertile men[35], or improve immune function related to the prevention and

treatment of age-associated diseases.[36] However, to date, no large clinical trials have verified these findings.

A preliminary study published in the Annals of Surgery found that the early administration of antioxidant supplementation using α-tocopherol and ascorbic acid reduces the incidence of organ failure and shortens ICU length of stay in this cohort of critically ill surgical patients.[37] More research on this topic is pending.

Dehydroascorbic acid, the main form of oxidized vitamin C in the body, was shown to reduce neurological deficits and mortality following stroke, due to its ability to cross the blood-brain barrier, while "the antioxidant ascorbic acid (AA) or vitamin C does not penetrate the blood-brain barrier".[38] In the study published by the Proceedings of the National Academy of Sciences in 2001, the authors concluded that such "a pharmacological strategy to increase cerebral levels of ascorbate in stroke has tremendous potential to represent the timely translation of basic research into a relevant therapy for thromboembolic stroke in humans". No such "relevant therapies" are available yet.

In January 2007 the US Food and Drug Administration approved a Phase I toxicity trial to determine the safe dosage of intravenous vitamin C as a possible cancer treatment for "patients who have exhausted all other conventional treatment options." Additional studies over several years would be needed to demonstrate whether it is effective. In February 2007, an uncontrolled study of 39 terminal cancer patients showed that, on subjective questionnaires, patients reported an increase in health, quality of life, and daily function after administration of high-dose intravenous vitamin C.[39] The

authors concluded that "Although there is still controversy regarding anticancer effects of vitamin C, the use of vitamin C is considered to be a safe and effective therapy to improve the quality of life of terminal cancer patients".

A team of University of California researchers demonstrated for the first time that vitamin C supplements can lower C-reactive protein (CRP)[40] levels in the blood. C-reactive protein is a marker of inflammation and chronic disease risk in humans. Chronic inflammation accompanied by low levels of CRP has been found in smokers, type 2 diabetics, hypertension and obese and overweight individuals. Another study showed Vitamin C given at the dose of 500 mg/day significantly reduced the Blood pressure and oxidized LDL cholesterol levels in hypertensive patients.[41]

Adverse effects

While being harmless in most typical quantities, as with all substances to which the human body is exposed, vitamin C can still cause harm under certain conditions.

Common side-effects

Relatively large doses of vitamin C (>10000 mg/day) may cause indigestion, particularly when taken on an empty stomach.

When taken in large doses, vitamin C causes diarrhea. In one trial, doses upto 6 grams of ascorbic acid were given to 29 infants, 93 children of preschool and school age, and 20 adults for more than 1400 days. With the higher doses, toxic manifestations were observed in five adults and four infants. The signs and symptoms in adults were nausea, vomiting, diarrhea, flushing of the face, headache, fatigue and disturbed sleep. The main toxic reactions in the infants were skin rashes.[42]

During the first month of pregnancy, high doses of vitamin C may suppress the production of progesterone from the corpus luteum. Progesterone, necessary for the maintenance of a pregnancy, is produced by the corpus luteum for the first few weeks, until the placenta is developed enough to produce its own source. By blocking this function of the corpus luteum, high doses of vitamin C (>6000 mg) is theorized to induce an early miscarriage. In a group of spontaneously aborting women at the end of the first trimester, the mean values of vitamin C were significantly higher in the aborting group. However, the authors point out that this relationship may not necessarily be a causal one.[43]

Chance of overdose

As discussed previously, vitamin C exhibits remarkably low toxicity. The LD_{50} (the dose that will kill 50% of a population) in rats is generally accepted to be 11,900 milligrams per kilogram when taken orally.[44] The LD_{50} in humans remains unknown, owing to medical ethics that preclude experiments which would put patients at risk of harm. However, as with all substances tested in this way, the LD_{50} is taken as a guide to its toxicity in humans and no data to contradict this has been found.

C-REACTIVE PROTEIN

C-reactive protein (CRP) is a plasma protein, an acute phase protein produced by the liver. It is a member of the pentraxin family of proteins

Genetics and biochemistry

The CRP gene is located on the first chromosome (1q21-q23). CRP is a 224 residue protein with a monomer molar mass of 25106 Da, and native cyclic pentamer mass of 125530 Da.

Function

CRP is a member of the class of acute phase reactants as its levels rise dramatically during inflammatory processes occurring in the body. This increment is due to a rise in the plasma concentration of IL-6, which is produced in macrophages, endothelial cells and T-cells. CRP binds to phosphorylcholine on microbes. It is thought to assist in complement binding to foreign and damaged cells and enhances phagocytosis by macrophages, which express a receptor for CRP. It is also believed to play an important role in innate immunity, as an early defense system against infections. The desirable levels of C-reactive protein should be less than 1 mg/dl in normal individuals.

Diagnostic use

CRP is used mainly as a marker of inflammation. Measuring and charting C-reactive protein values can prove useful in determining disease progress or the effectiveness of treatments. Blood, usually collected in a serum-separating tube, is analyzed in a medical laboratory or at the point of testing.

Various analytical methods are available for CRP determination, such as ELISA, immunoturbidimetry, rapid immunodiffusion and visual agglutination.

C-REACTIVE PROTEIN AND HYPERTENSION AND CARDIOVASCULAR RISKS:

Several studies showed that there is increased incidence of complications of hypertension in patients with elevated C-reactive protein levels.[45]

Cardiovascular disease (CVD) is currently the leading cause of death and disability in the developed world, and will soon overtake infectious disease as the pre-eminent cause of death worldwide.[46] Atherosclerosis is the most important contributor to this substantial disease burden. Whereas previously considered a bland process, our current understanding of atherosclerosis suggests that it is a dynamic and progressive disease arising from a combination of endothelial damage/dysfunction[47], thrombosis and inflammation.[48]

A substantial body of evidence has suggested that four modifiable risk factors such as smoking, diabetes, hypertension and hyperlipidaemia account for a significant proportion of CVD, and that reduction of these risk factors leads to improved morbidity and mortality. However, these traditional risk factors are not present in up to half of patients presenting with a clinical manifestation of CVD. Hence, there has been enormous interest in the identification of other measurable CVD risk factors in persons without overt disease. This would allow for the introduction of targeted pre-emptive preventive measures to prevent future cardiovascular events. Several novel candidate markers of potential use have been identified and include C-reactive protein (CRP), lipoprotein (a), homocysteine and fibrinogen.

CRP has emerged as a strong, robust and independent risk factor for CVD that appears to have significant clinical utility. It is a circulating acute phase reactant named initially for its capacity to bind to the c-polysaccharide of Streptococcus pneumoniae, and is synthesized primarily by the liver in response to IL-6 and IL-1β. As a risk assessment tool, it has several good points — it is very stable, with very little difference in values between fresh or

frozen plasma and has a long half-life of upto 20 h.[49] It normally circulates at very low levels, but acute inflammatory processes induce marked hepatic synthesis of CRP, which can induce a 100-fold serum increase.[50] Evidence also shows that patients with hypertension have increased levels of C-reactive protein levels since inflammatory process and endothelial dysfunction contributes to the development and severity of hypertension.[51]

Evidence has shown that, even in apparently healthy subjects, there is good and consistent significant relationship (in all populations) between baseline CRP levels and risk of future cardiovascular events (stroke, peripheral vascular disease, sudden cardiac death and myocardial infarction).[52] In those with existing CVD, it has been shown to predict future cardiovascular events including recurrent ischaemia, atrial fibrillation, death, stroke and percutaneous coronary intervention.[53] Elevated CRP also appears to correlate with softer plaques that are more prone to rupture.[54]

It is likely that CRP is more than simply an inflammatory marker of increased CVD risk, as deposits of CRP have been demonstrated, on immunohistochemical staining, in the vascular wall of atherosclerotic plaques, where it is co-localized with the terminal complement complex and appears to be involved in foam cell formation.[55]

Of note, the investigation of arterial stiffness has gathered pace in recent years with the development of readily available noninvasive assessment techniques. Previous studies have shown increased large artery stiffness to be an additional predictor of both atherosclerosis and cardiovascular risk.[56]

Two complementary studies further supports the value of CRP as a surrogate marker for severity of hypertension and atherosclerosis. In the one study, researchers add to an increasing body of evidence[58] demonstrating a significant relationship between CRP and stiffness of large arteries (as an early marker of severity of hypertension and atherosclerosis[59]). In this study, radial artery pulse wave activity was studied in 391 asymptomatic, apparently low-risk patients (mean age 50.9 years, only 10% smokers and 16% on hypertensive treatment) undergoing primary prevention screening. In the second much smaller study of 83 higher risk hypertensive patients.

Another study have shown a correlation between CRP and atherosclerosis of the abdominal aorta and renal arterial tree. Taken together, these two papers lend further support to the hypothesis that inflammation within the arterial wall of large arteries (as manifested by increased levels of CRP) exerts its vascular effects by decreasing large artery elasticity and increasing its stiffness, both markers of severity of hypertension and developing atherosclerosis.[60]

It have been proved that inflammation may be involved in the initiation development and severity of hypertension, with the exertion of pro inflammatory actions through several mediators, including adhesion molecules, chemokines, growth factors, heat shock proteins, endothelin-1 and angiotensin. Indeed, even a persistent low-grade inflammatory state could result in a high but within the 'normal range' concentrations of inflammatory cytokines. Certainly, low-grade inflammation has been associated with other components of the metabolic syndrome, and endothelial damage/dysfunction.

By impairing the capacity of the endothelium to generate vasodilating factors, particularly nitric oxide (NO), elevated cytokines may cause endothelial dysfunction, chronic impaired vasodilatation and hypertension.[61] Inflammation is also intimately related to thrombogenesis, which is of relevance since the main complications of hypertension (stroke, myocardial infarction) are mainly thrombosis-related. The possibility that hypertension may be an inflammatory disease may have implications for novel therapeutic strategies to decrease the morbidity as well as mortality of hypertension, and treat hypertensive target organ damage. Certainly, prospective data are required to assess the effects of interventions and impact on prognosis.

The process of atherogenesis starts in early childhood and hypertension is simply one associated risk factor. It is therefore possible that inflammatory parameters are abnormal in essential hypertension and may simply indicate sub-clinical or early vascular disease or atherosclerosis. Many recent studies have suggested a direct relationship between CRP and hypertension.[62,63,64,65,66,67]

It is more likely that the inflammation remains one part of the complex pathophysiology linking hypertension to vascular disease. This would help our understanding and management of hypertension, which continues to be a major disease risk factor and burden on our healthcare resources.[68,69]

ROLE OF VITAMIN C IN HYPERTENSION AND CARDIO VASCUALAR RISKS

Heart Disease

Vitamin C has multiple actions that can reduce the risk of heart disease. Two recent studies have found that 500 mg daily can significantly reduce blood pressure. In a study 38 people with mild to moderate hypertension, researchers of the Boston University School of Medicine, reported that 500 mg daily of vitamin C supplements reduced blood pressure by almost 10 percent in just one month.[70]

A separate study, by British researchers., of the Glenfield Hospital, Leicester, England, found that 500 mg daily of vitamin C reduced blood pressure by an average of 6 mmHg in 40 elderly men and women after three months.[70] Researchers have also discovered that vitamin C can improve "endothelial dysfunction," a risk factor for heart disease characterized by stiff blood vessel and reduced blood flow. Diets high in a combination of saturated fat and refined carbohydrates increase endothelial dysfunction. British researchers determined that 500 mg/day of vitamin C could improve blood vessel flexibility.[71]

Stroke

Several studies have found that vitamin C can reduce the risk of stroke - and limit brain damage from strokes. In a study of 2,100 Japanese men and women, researchers of the Osaka City University Medical School, noted that subjects with the highest blood levels of vitamin C at the beginning of the

study, suggestive of long-term vitamin C consumption, had the lowest risk of stroke after age 40. People above the age of 64 with high vitamin C levels were 41 percent less likely to suffer a stroke compared with those who had the lowest vitamin C levels. [72]

A recent study found that the oxidized form of vitamin C - that is, the type formed after fighting free radicals - efficiently enters the brain and is particularly good at minimizing the brain damage. In an animal study, researchers at Columbia University, New York City, found that in high doses dehydroascorbic acid, which the body normally makes from vitamin C (and can be converted back to vitamin C), reduced stroke damage by upto 95% in laboratory mice. The researchers recommended that dehydroascorbic acid be used as a "drug" in stroke patients.

VITAMIN C IN THE REDUCTION OF C-REACTIVE PROTEIN LEVELS AND BLOOD PRESSURE

Researchers from the Boston University School of Medicine and Oregon State University studied 39 patients with mild to moderate hypertension. About half of the patients took daily doses of 500 mg of vitamin C, also known as ascorbic acid, while the other half took a placebo. After one month, the average blood pressure of patients who took vitamin C dropped significantly more than that of patients in the placebo group, or 9.1 percent compared to 2.7 percent, respectively.[73] Vitamin C reduces the production of C-Reactive protein levels from liver, thereby decreasing the incidence of occurrence of future cardiovascular risks and cerebrovascular accidents which occurs due to hypertension.

Studies have also shown that vitamin C also improves Endothelial dysfunction which commonly occurs in hypertensive patients. Vitamin C also reduces arterial stiffness and improves the vascular flexibility thereby decreases the blood pressure. Vitamin C , by its anti oxidant property decreases the degradation of Nitric oxide, a potent vasodilator, which occurs during oxidative stressful conditions such as hypertension thereby decreases the blood pressure in hypertensive individuals. None of the previous studies have shown the combined effect of vitamin C in the reduction of C reactive protein levels and blood pressure. Hence, this study was undertaken to find out the efficacy and tolerability of vitamin C as an add-on therapy to standard anti hypertensive therapy in the reduction of C-reactive protein levels and blood pressure in patients with mild to moderate hypertension.

OBJECTIVES

OBJECTIVES

Primary Objective :

To evaluate the efficacy of Vitamin C as an add-on therapy to the standard anti-hypertensive regimen in the reduction of blood pressure and C- reactive protein levels in mild to moderate hypertension.

Secondary Objective :

To evaluate the tolerability of Vitamin C as an add-on therapy to the standard anti-hypertensive regimen in the management of mild to moderate hypertension

METHODOLOGY

Methodology

The study was undertaken in mild to moderate hypertensive patients to find out the efficacy and tolerability of vitamin C as an add-on therapy to the standard anti-hypertensive regimen in the reduction of blood pressure and C-reactive protein levels. The study was conducted in Institute of Pharmacology, Madras Medical College, Chennai in collaboration with Department of Internal medicine, Government General Hospital, Chennai.

STUDY DESIGN :

This study was an open-label, randomized, comparative , prospective, parallel group study.

STUDY CENTRE :

Hypertension clinic,

Department of Internal Medicine,

Madras Medical College,

Government General Hospital,

Chennai.

STUDY PERIOD :

The study was carried out from November 2005 to December 2006.

STUDY DURATION :

6 months for each patient

STUDY POPULATION :

Patients attending the Out patient department of Hypertension clinic, Department of Internal Medicine, Government General Hospital, Chennai

SAMPLE SIZE :

120 patients

(30 patients in each group)

STUDY PROCEDURE :

Inclusion criteria :

- Patients of either sex
- Patients in the age group of 18 – 65 years
- Patients with mild to moderate hypertension

(Mild hypertension : systolic blood pressure 140 – 159 mm Hg and diastolic blood pressure 90 – 99 mm Hg, Moderate hypertension : systolic blood pressure 160 – 179 mm Hg and diastolic blood pressure 100- 109mm Hg)

- Patients with C reactive protein levels more than 10 mg /dl
- Patients with Body Mass Index (BMI) of 18 – 25
- Patients willing to give written informed consent

Exclusion criteria :

- Patients with history of septic arthritis, meningitis, pneumonia
- Patients with history of pyelonephritis, tonsillitis, otitis media
- Patients with upper respiratory tract infection
- Patients with any other active infection
- Patients with rheumatoid arthritis, acute pancreatitis
- Patients with any history of surgery in the recent past 3 months
- Patients with history of malignancies
- Patients with history of myocardial infarction
- Patients with evidence of gastrointestinal tract, renal, endocrine, cardiovascular abnormalities and any other major systemic illness
- Pregnant and lactating women
- Patients who cannot comply with the protocol
- Patients not willing to give written informed consent

The study commenced after obtaining approval from the Institutional Ethical Committee.

ENROLLMENT VISIT :

Patients who attended the Out patient department of Hypertension Clinic, Department of Internal Medicine, Government General Hospital, Chennai were explained in detail about the study procedure, purpose and its benefits.

They were explained about the following :

The purpose of this study was to

- Achieve better blood pressure reduction
- Reduce complications
- Improve the quality of life in hypertensive patients

Written informed consent was obtained from patients willing to participate in the study, in the prescribed format in the regional language prior to the performance of the study procedures. If the patient is illiterate, left thumb impression was sought. This was done in the presence of impartial witness. Patients advised to come on next day at 8.00 A.M on empty stomach for screening procedure.

SCREENING (Visit 0):

Patients who gave written informed consent for participation in the study were screened by detailed medical history, blood pressure monitoring , estimation of C-reactive protein levels, physical and systemic examination, baseline demographic characteristics were recorded. Blood was drawn for determining the hematological and serum biochemical tests. 529 patients were screened.

LABORATORY INVESTIGATIONS :

The following laboratory investigations were done at screening

1. Complete Hemogram :

a. Hemoglobin

b. Total WBC count

c. Neutrophil count

d. Lymphocyte count

e. Red Blood Cell count.

2. Blood Biochemistry

a. Blood sugar

b. Blood urea

c. Serum creatinine

3. Liver Function Tests

a. SGOT

b. SGPT

c. SAP

d. Total bilirubin

e. Total protein

f. Albumin

4. Urine Analysis

5. C-reactive protein levels estimation

Sample collection for Serum C-reactive protein level estimation and other hematological and biochemical parameters estimation

The subjects were asked to come on an empty stomach to the Outpatient Department of Hypertension Clinic, Government General Hospital

at 8.00 A.M. on the sample collection day. On arrival at the hospital the subject's vital signs were recorded and ascertaining that condition of the subject was normal. The blood samples for determining serum C-reactive protein levels and other biochemical and hematological parameters were collected into the blood collection tubes by venepunture. At each sampling 10ml of blood was drawn.All the vital signs were monitored at the end of the sampling and only when both the patient and clinician are confident, the subjects were allowed to go from the out patient department of the Hypertension clinic where the study was conducted. The serum C-reactive protein levels was estimated using Enzyme Linked Immuno Sorbent Assay (ELISA) and other hematological and biochemical parameters were estimated.

RECRUITMENT AND GROUPING :

Among 529 patients screened, 120 patients who fulfilled the inclusion and exclusion criteria were recruited for the study. The recruited 120 patients were randomized into four groups each consisting of 30 patients.

GROUPING :

- GROUP I : Enalapril 5 mg BD
- GROUP II : Enalapril 5 mg BD + Vitamin C 100 mg OD
- GROUP III : Enalapril 5 mg BD + Vitamin C 250 mg OD
- GROUP IV : Enalapril 5 mg BD + Vitamin C 500 mg OD

STUDY VISITS :

VISIT 1 (Base line) :

Out of 529 patients screened, 120 patients with systolic blood pressure in the range of 140 – 179 mm Hg and diastolic blood pressure in the range of 90 – 109 mm Hg with C-reactive protein levels in the range of 10 – 12 mg/dl were recruited for the study. The following procedures were done at visit I.

Randomization :

- Randomization into four groups
    - Each group consisting of 30 patients
    - Group I patients were given Enalapril 5 mg BD
    - Group II patients were given Enalapril 5 mg BD along with Vitamin C 100 mg OD
    - Group III patients were given Enalapril 5 mg BD along with Vitamin C 250 mg OD
    - Group IV patients were given Enalapril 5 mg BD along with Vitamin C 500 mg OD
    - Patient were given medication for two weeks
    - Instructed to come fortnightly to collect the medication
    - Patients were instructed to bring the empty foils at the end of 2 weeks to check the patients compliance
    - Patients blood pressure was recorded
    - Detailed medical history and clinical examination was done
    - Blood samples were collected for the estimation of C-reactive protein levels and routine hematological and

biochemical parameters.

- Patients were advised to report to the investigator as soon as possible in case of occurrence of any adverse effects
- Patients were instructed to report to the investigator in case of occurrence of any other illness and intake of other medications for the same.

VISIT 2 (At the End of 1st month) :

- Patients compliance was checked.
- Patients blood pressure was recorded.
- Detailed medical history and clinical examination were done.
- Blood samples were collected for the estimation of C-reactive protein levels and routine hematological and biochemical parameters.
- Medications were issued to the patients for 2 weeks.
- Instructed to come fortnightly to collect the medication.
- Patients were advised to report to the investigator as soon as possible in case of occurrence of any adverse effects.
- Patients were instructed to report to the investigator in case of occurrence of any other illness and intake of other medications for the same.

VISIT 3 (At the End of 3rd month) :

- Patients blood pressure was recorded.
- Detailed medical history and clinical examination were done.
- Blood samples were collected for the estimation of C-reactive protein levels and routine hematological and biochemical parameters.
- Study medications were issued to the patients for 2 weeks.
- Instructed to come fortnightly to collect the medication.
- Patients were instructed to bring the empty foils at the end of 2 weeks to check the patients compliance.
- Patients were advised to report to the investigator as soon as possible in case of occurrence of any adverse effects.
- Patients were instructed to report to the investigator in case of occurrence of any other illness and intake of other medications for the same.

VISIT 4 (At the End of 6th month) :

- Patients blood pressure was recorded.
- Detailed medical history and clinical examination were done.
- Blood samples were collected for the estimation of C-reactive protein levels and routine hematological and

biochemical parameters.

- Instructed to come fortnightly to collect the medication for 2 weeks.
- Patients were instructed to bring the empty foils at the end of 2 weeks to check the patient's compliance .
- Patients were advised to report to the investigator as soon as possible in case of occurrence of any adverse effects.
- Patients were instructed to report to the investigator in case of occurrence of any other illness and intake of other medications for the same.
- Patients were instructed to attend the Out Patient department of Hypertension clinic to get the medications regularly.

This study was undertaken to find out the efficacy and tolerability of vitamin C as an add-on therapy to the standard anti hypertensive therapy in the reduction of blood pressure and C-reactive protein levels in the patients with mild to moderate hypertension.

RESULTS

RESULTS :

Out of 529 patients screened, 120 patients who fulfilled the inclusion and exclusion criteria were recruited for the study. They were randomized into four groups, Group I, Group II, Group III and Group IV, each consisting of 30 patients.

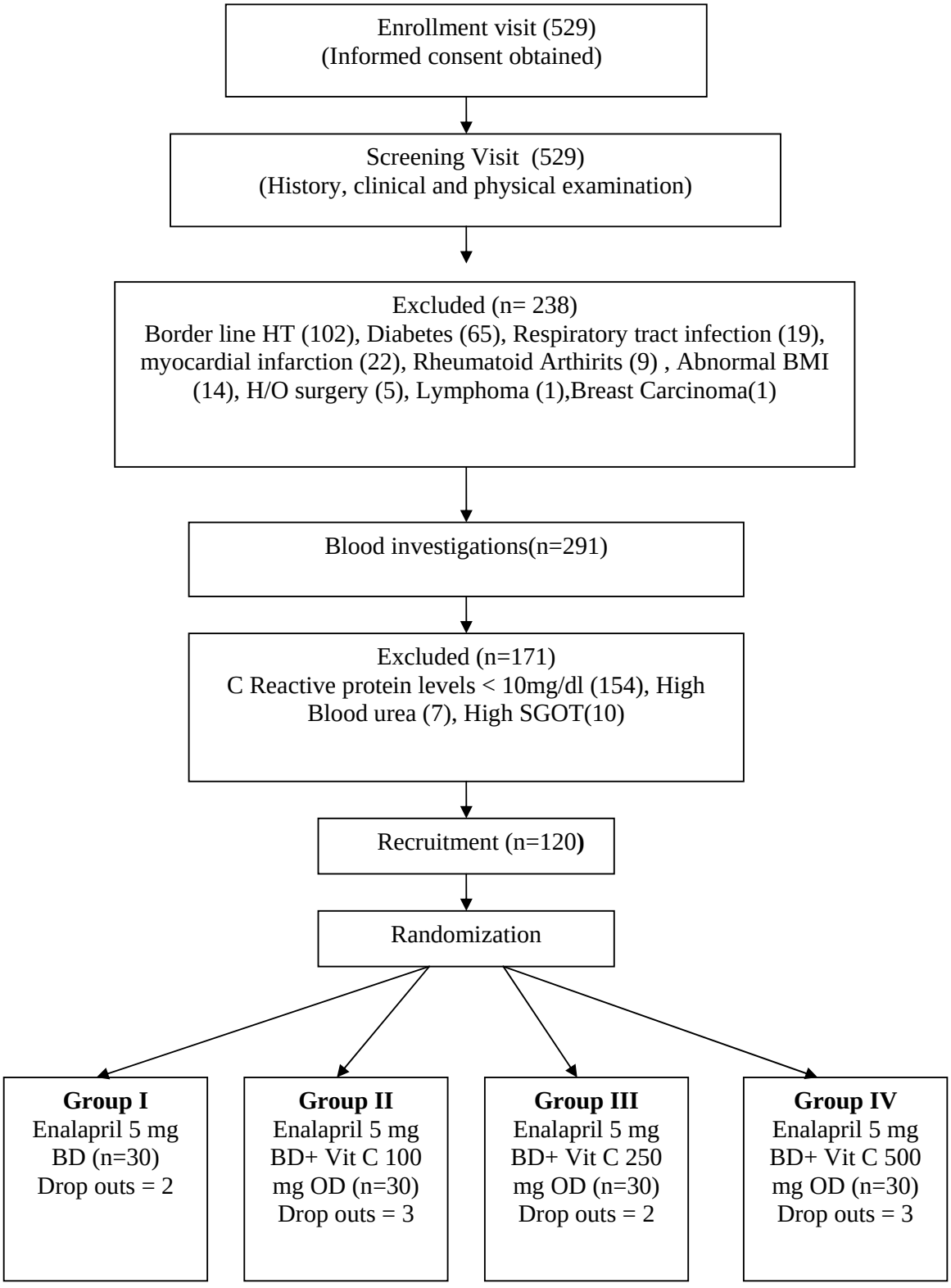
Group I received standard anti hypertensive treatment Enalapril 5 mg BD, Group II received Vitamin C 100 mg OD along with Enalapril 5 mg BD, Group III received Vitamin C 250 mg OD along with Enalapril 5 mg BD and Group IV received Vitamin C 500 mg OD along with Enalapril 5 mg BD for a period of six months for each patient.

Parameters were assessed at the baseline, at the end of 1^{st} month, at the end of 3^{rd} month and at the end of 6^{th} month of study. Only 110 patients (28 in Group I , 27 in Group II, 28 in Group III and 28 in Group IV) completed the study.

STATISTICAL ANALYSIS :

Statistical analysis was done using One way Anova for comparison between groups and Bonferonni's test for multiple comparison. Analysis of adverse events was done using Chi – Square test.

CLINICAL STUDY FLOWCHART



DROP OUTS :

SL NO	GROUPS	NO OF DROP OUTS
1	Group I	2
2	Group II	3
3	Group III	2
4	Group IV	3

Reasons for Drop Outs :

1. In Group I, one patient didn't turn up after one month of study and the remaining one patient not willing to continue the study after 2 months.
2. In Group II, two patients didn't turn up after 1 month of study commencement and one patient was not willing to continue in the study after 2 months.
3. In Group III, two patients lost to follow up for the study after one month period.
4. In Group IV, two patients lost to follow up after one month and one patient withdrew his willingness to participate in the study after one month.

AGE DISTRIBUTION

Table 1 :

GROUPS	N	Mean	Std. Deviation	ANOVA F-test
GROUP I	28	44.96	7.613	F=0.49 P=0.69 Not Significant
GROUP II	27	46.30	8.203	
GROUP III	28	47.50	7.550	
GROUP IV	27	46.04	7.881	
Total	110	46.20	7.758	

Figure 1 :

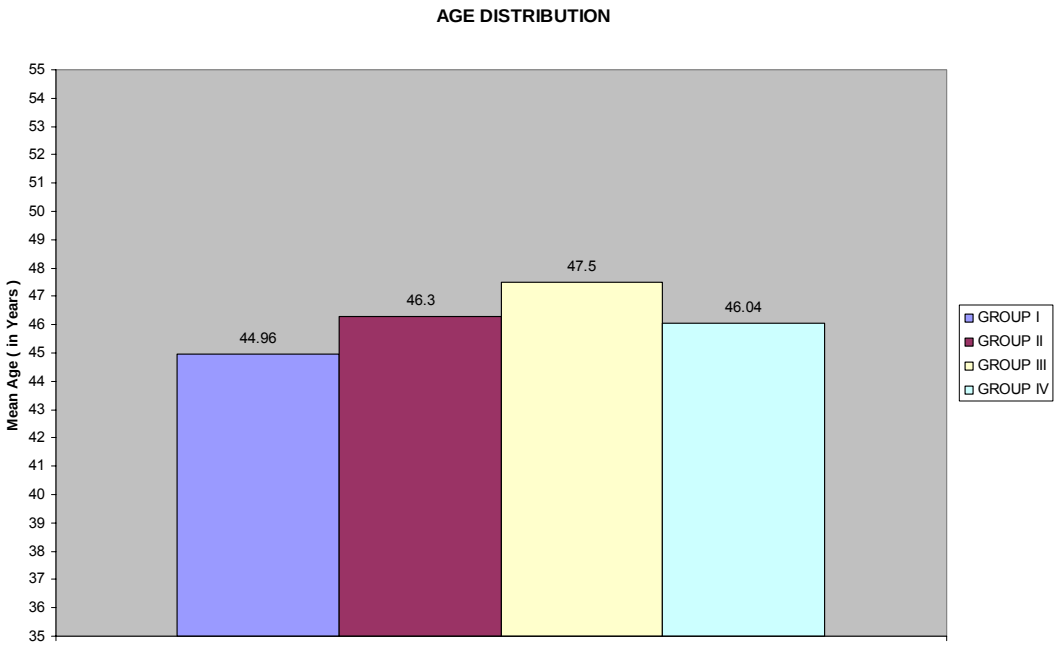


Table 1 :

shows

- The number of patients in study groups I, II, III & IV
- Mean age was evenly distributed among the groups

There was **no statistical significant difference** among the study groups.

Figure 1 : shows the diagrammatic representation of the age distribution in study groups .

BODY MASS INDEX

Table 2 :

GROUPS	N	Mean	Std. Deviation	ANOVA F-test
GROUP I	28	21.057	1.8136	F=0.80 P=0.49 Not significant
GROUP II	27	20.841	1.8952	
GROUP III	28	20.457	1.9667	
GROUP IV	27	20.393	1.7444	
Total	110	20.688	1.8524	

Figure 2 :

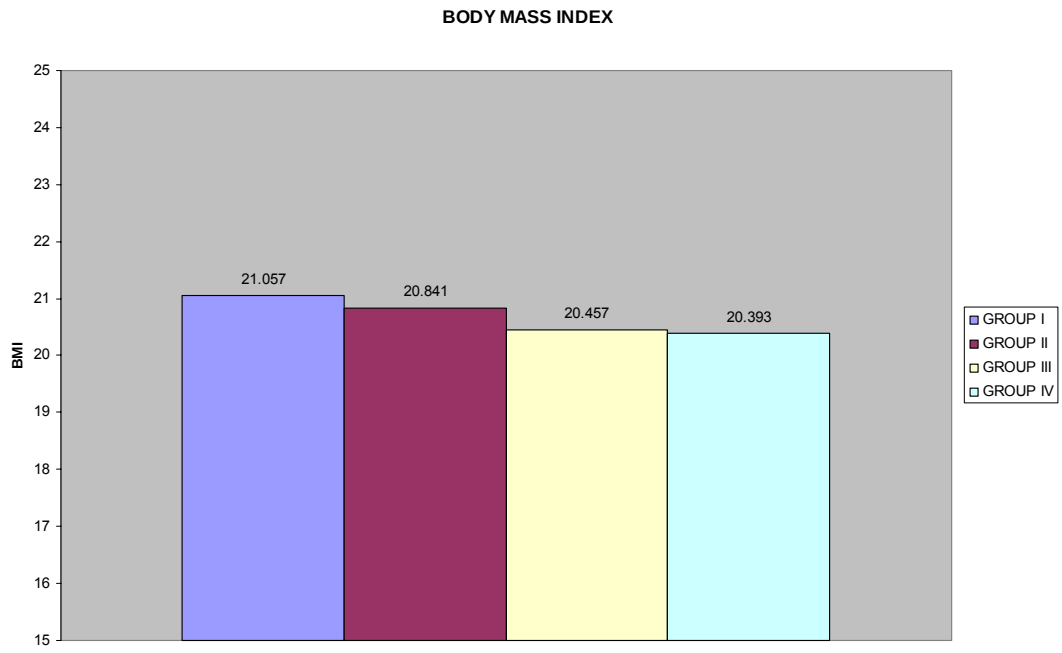


Table 2 : shows the mean body mass index of patients in each study group.

There was **no statistical significant difference** among groups regarding BMI.

Figure 2 : shows the diagrammatic representation of the BMI of patients in each group.

SEX DISTRIBUTION

Table 3 :

GROUPS	SEX				CHI SQUARE TEST
	MALE		FEMALE		
	n	%	n	%	
GROUP I	22	78.6%	6	21.4%	$\chi 2=0.44$
GROUP II	20	74.1%	7	25.9%	P = 0.91 (not significant)
GROUP III	22	78.6%	6	21.4%	
GROUP IV	22	81.5%	5	18.5%	

Figure 3 :

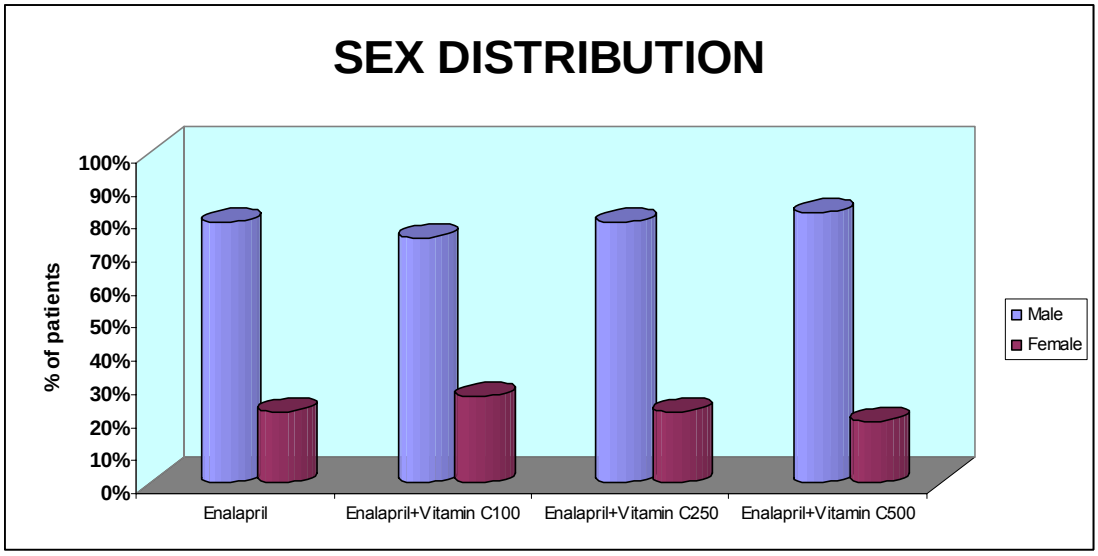


Table 3 : shows the sex distribution in the study groups.

Statistical analysis was done with Chi square test. There was no statistical significant difference among groups regarding sex distribution.

Figure 3 : shows the bar diagram of sex distribution among the groups

COMAPARISON OF REDUCTION OF SYSTOLIC BLOOD PRESSURE

Table 4 :

Parameter	Groups								Test of significance	Bonferonni test Multiple comparison
	GROUP I		GROUP II		GROUP III		GROUP IV			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
SBP_base Line	159.36	6.18	155.93	7.41	157.36	7.40	158.74	6.40	F=1.35 P=0.26 (NS)	NS
SBP_1st month	153.86	5.44	149.78	6.36	148.07	6.77	141.04	7.09	F=21.28 P=**0.04** **(S)**	4 Vs 1,2,3
SBP_3rd month	147.93	5.64	142.52	7.56	141.79	7.04	129.70	3.50	F=46.28 P=**0.001** **(S)**	4 Vs 1,2,3
SBP_6th month	139.21	7.57	124.52	18.97	121.57	20.37	119.48	3.07	F=9.20 P=**0.001** **(S)**	4 Vs 1,2,3
Significance	F=53.0 P=**0.001**(S)		F=38.9 P=**0.001**(S)		F=31.1 P=**0.001**(S)		F=270.8 P=**0.001**(S)			

Figure 4 :

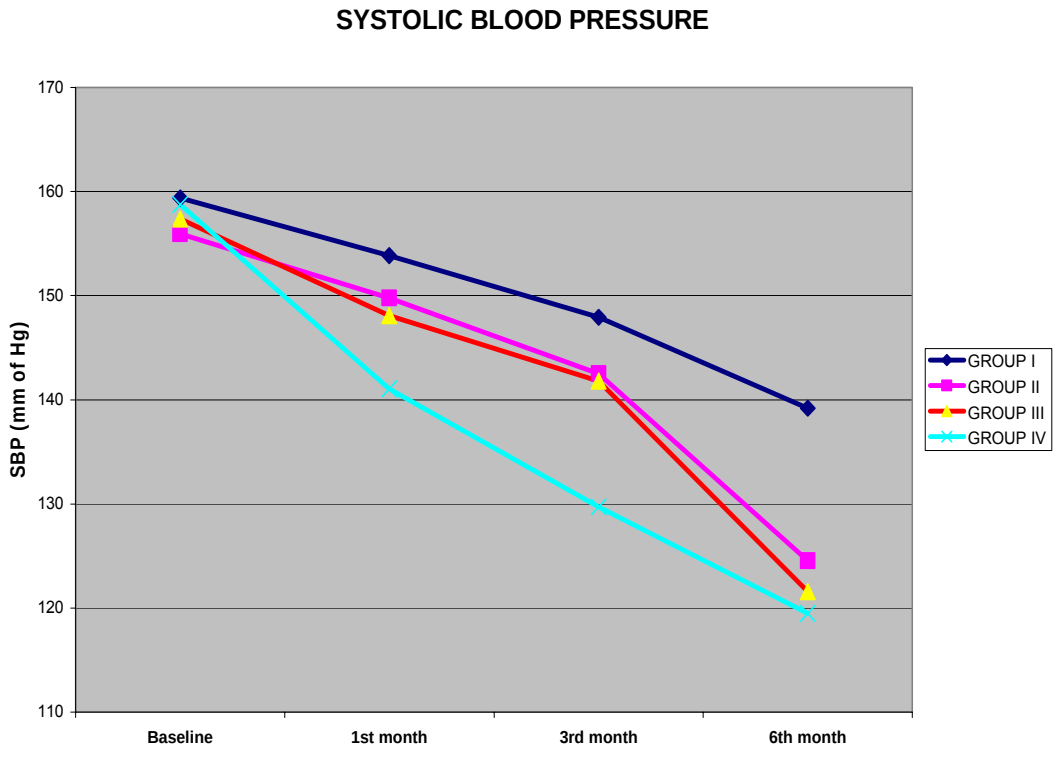


Table 4 : shows the Mean **SYSTOIC BLOOD PRESSURE** in each group at baseline, at the end of 1st month, of 3rd month and 6th month.

At the baseline

There was **no statistical significant difference** among groups at baseline.

At the end of 1st month

BONFERRONI T- test shows **statistical significant difference** in **Group IV** when compared with Group I,II & III at end of 1st month

At the end of 3rd month

BONFERRONI T- test shows **statistical significant difference in Group IV** when compared with **Group I,II & III**

At the end of 6th month

BONFERRONI T- test shows **statistical significant difference** in **Group IV** when compared with Group **I, II** & **III**

Figure 4 : shows the diagrammatic representation of the mean SYSTOLIC BLOOD PRESSURE in all the study groups at base line, at the end of 1st month, 3rd month and 6th month.

PERCENTAGE REDUCTION OF SYSTOLIC BLOOD PRESSURE AMONG GROUPS

Table 5 :

	1^{ST} MONTH	3^{RD} MONTH	6^{TH} MONTH
GROUP I	3.45%	7.17%	12.64%
GROUP II	3.94%	8.60%	20.14%
GROUP III	5.9%	8.89%	22.74%
GROUP IV	11.15%	18.29%	24.73%

Figure 5 :

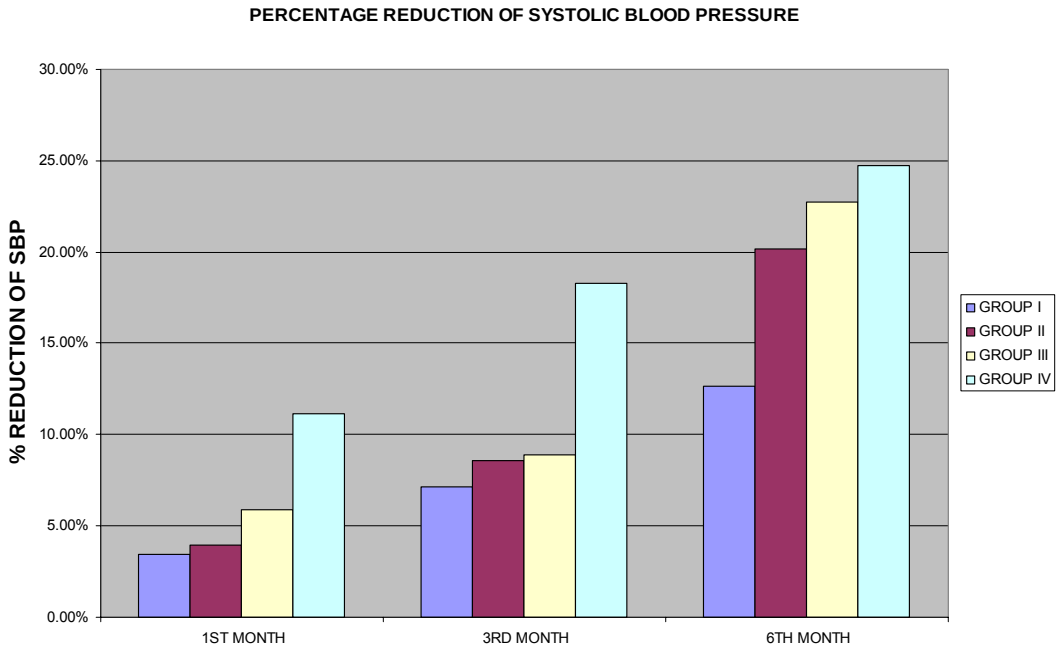


Table 5 :

Shows the percentage reduction of systolic blood pressure from baseline, at the end of 1st month, 3rd month and 6th month among the study groups

Figure 5 :

Shows the diagrammatic representation of the percentage reduction of systolic blood pressure from baseline, at the end of 1st month, 3rd month and 6th month among the study groups

COMPARISON OF REDUCTION OF DIASTOLIC BLOOD PRESSURE AMONG GROUPS

Table 6 :

Parameters	Group								Significance	Bonferonni test Multiple comparison
	GROUP I		GROUP II		GROUP III		GROUP IV			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
DBP_base Line	90.71	3.90	90.22	3.20	91.07	3.15	90.89	3.86	F=0.29 P=0.83(NS)	NS
DBP_1st month	86.50	4.17	85.52	3.12	84.36	3.13	83.59	3.18	F=3.17 P=0.07(NS)	NS
DBP_3rd month	84.29	3.76	83.22	2.90	82.79	2.90	78.33	2.35	F=19.5 P=**0.04**(S)	4 Vs 1,2,3
DBP_6th month	81.21	4.40	80.26	3.38	80.01	3.46	76.59	2.41	F=11.3 P=**0.001**(S)	4 Vs 1,2,3
Significance	F=27.1 P=**0.001**(S)		F=38.8 P=**0.001**(S)		F=52.4 P=**0.001**(S)		F=118.2 P=**0.001**(S)			

Figure 6 :

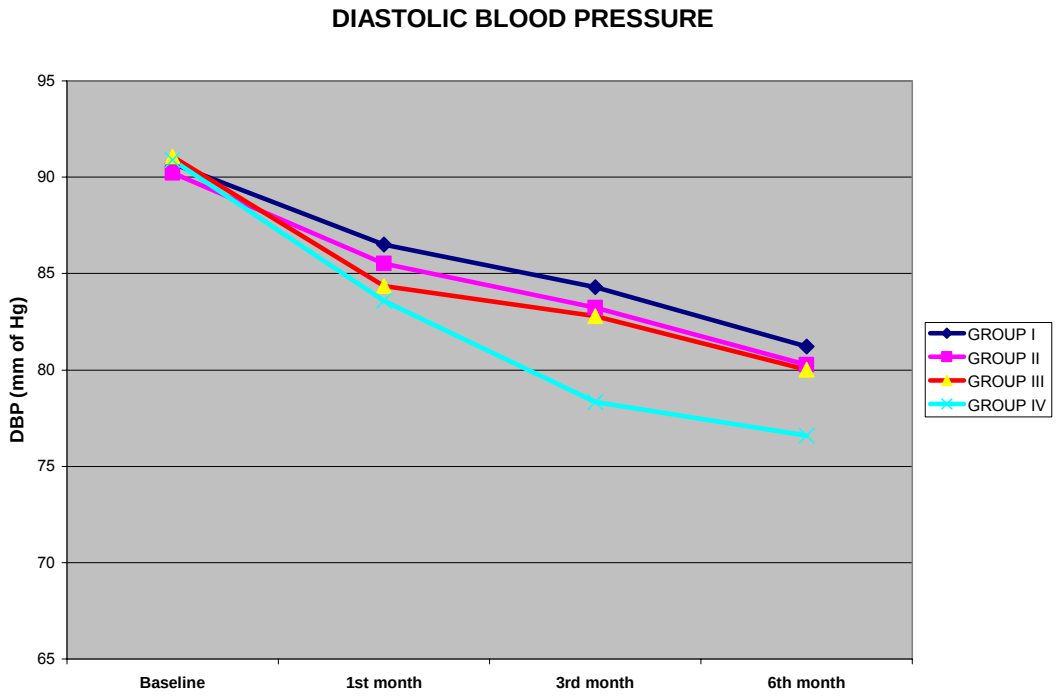


Table 6 : shows the Mean **DIASTOLIC BLOOD PRESSURE** in each group at baseline, at the end of 3rd month and 6th month.

At the baseline

There was **no statistical significant difference** among groups at baseline.

At the end of 1st month

BONFERRONI T- test shows **no statistical significant difference** between Groups

At the end of 3rd month

BONFERRONI T- test shows **statistical significant difference in Group IV** when compared with Group **I,II** & **III**

At the end of 6th month

BONFERRONI T- test shows **statistical significant difference** in **Group IV** when compared with Group **I, II** & **III**

Figure 6 : shows the diagrammatic representation of the mean DIASTOLIC BLOOD PRESSURE in all the study groups at base line, at the end of 1st month, at the end of 3rd month and 6th month.

PERCENTAGE REDUCTION OF DIASTOLIC BLOOD PRESSURE

Table 7 :

	1^{ST} MONTH	3^{RD} MONTH	6^{TH} MONTH
GROUP I	4.64%	7.08%	10.47%
GROUP II	5.21%	7.76%	11.04%
GROUP III	7.37%	9.09%	11.27%
GROUP IV	8.03%	12.72%	15.73%

Figure 7 :

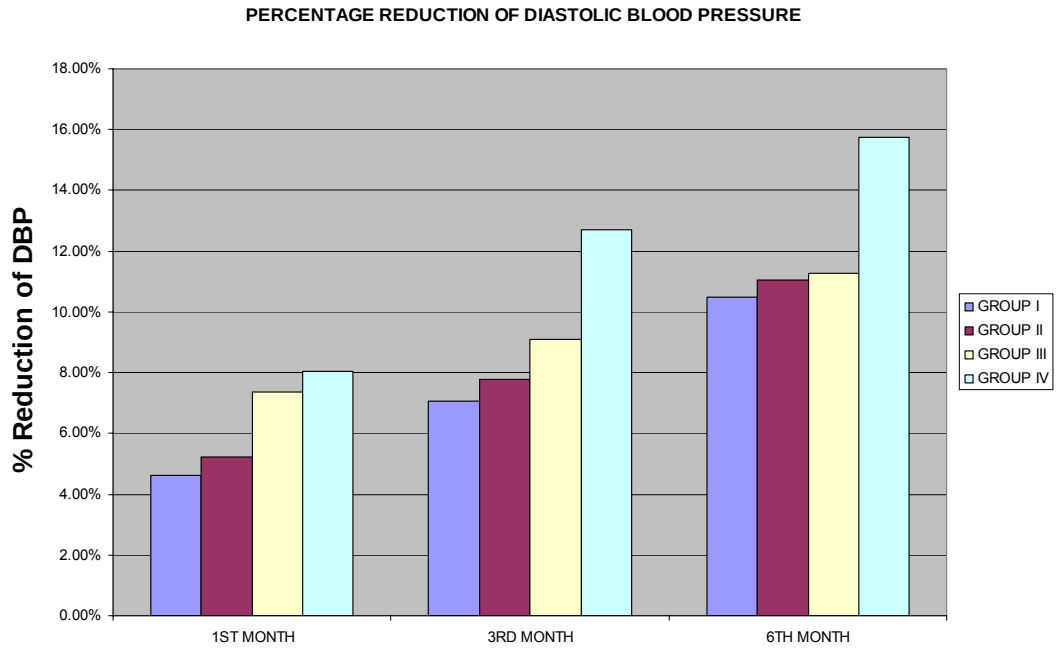


Table 7 :

Shows the percentage reduction of diastolic blood pressure from baseline, at the end of 1st month, 3rd month and 6th month among the study groups

Figure 7 :

Shows the schematic representation of the percentage reduction of diastolic blood pressure from baseline, at the end of 1st month, 3rd month and 6th month among the study groups

COMPARISON OF REDUCTION OF C REACTIVE PROTEIN LEVELS BETWEEN GROUPS

Table 8 :

Parameters	Group								Significance	Bonferonni test Multiple comparison
	GROUP I		GROUP II		GROUP III		GROUP IV			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
CRP_base Line	11.15	.38	11.22	.36	11.24	0.41	11.26	0.51	F=0.33 P=0.81(NS)	NS
CRP_1st month	11.12	.32	10.32	.42	6.77	1.29	5.69	1.26	F=20.99 P=**0.02**(S)	4 Vs 1,2,3
CRP_3rd month	11.11	.40	9.47	.50	5.08	0.96	1.29	0.96	F=93.81 P=**0.001**(S)	4 Vs 1,2,3
CRP_6th month	11.09	.38	8.39	.50	2.72	0.57	0.04	0.08	F=137.45 P=**0.001**(S)	4 Vs 1,2,3
Significance	F=3.06 P=0.27(NS)		F=19.58 P=0.07(NS)		F=46.92 P=**0.03**(S)		F=100.2 P=**0.001**(S)			

Figure 8 :

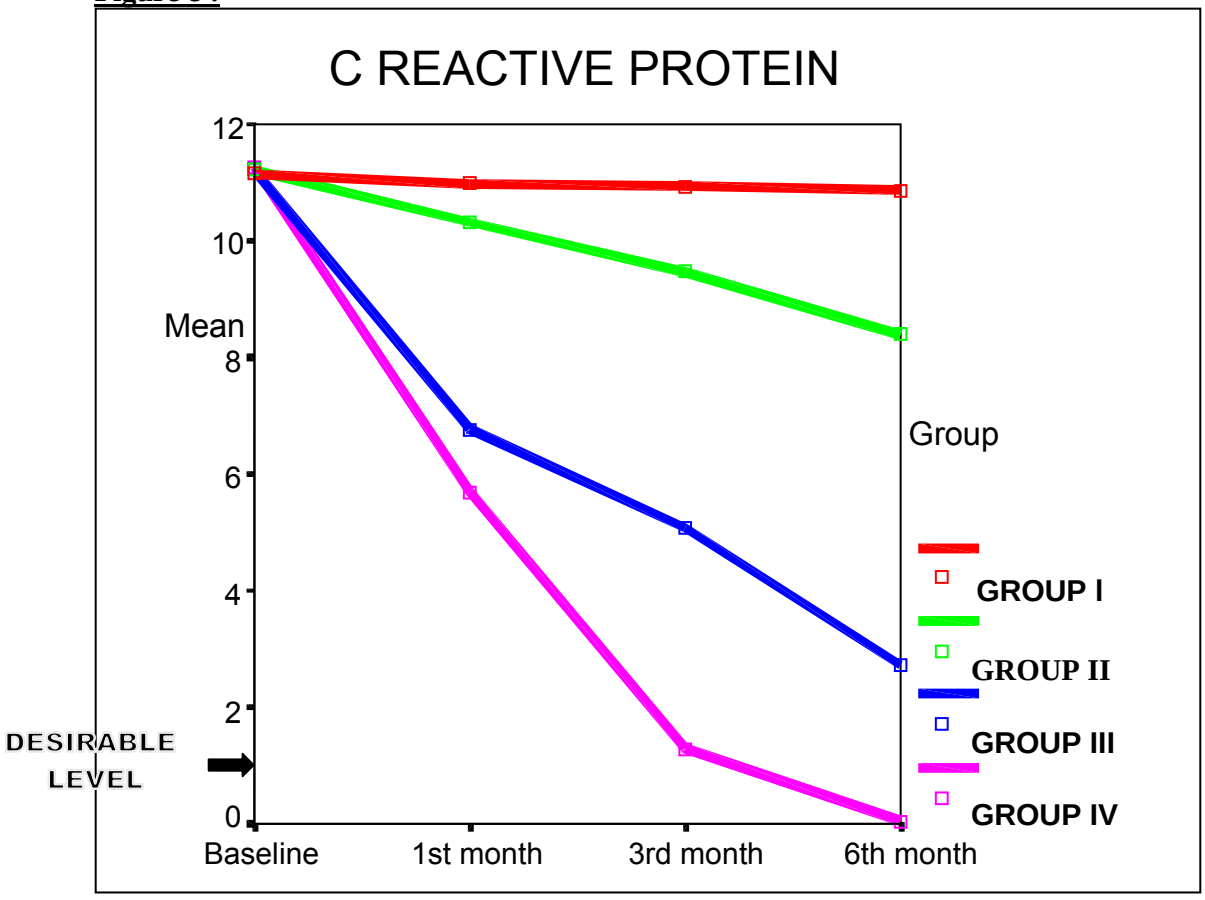


Table 8 : shows the mean C REACTIVE PROTEIN LEVELS in each group at baseline, at the end of 1st month, 3rd month and 6th month.

At the baseline

There was **no statistical significant difference** among groups at baseline.

At the end of 1st month

BONFERRONI T- test shows **statistical significant difference of in Group IV** when compared with **Group I, II & III**

At the end of 3rd month

BONFERRONI T- test shows **statistical significant difference of in Group IV** when compared with **Group I, II & III**

At the end of 6th month

BONFERRONI T- test shows **statistical significant difference of in Group IV** when compared with **Group I, II & III**

Figure 8 : shows the diagrammatic representation of the mean C REACTIVE PROTEIN LEVELS in all the study groups at base line, at the end of 1st month, 3rd month and 6th month.

PERCENTAGE REDUCTION OF C REACTIVE PROTEIN LEVELS

Table 9 :

	1ST MONTH	3RD MONTH	6TH MONTH
GROUP I	0.27%	0.36%	0.54%
GROUP II	8.02%	15.6%	25.22%
GROUP III	39.77%	54.8%	75.8%
GROUP IV	49.47%	88.54%	99.64%

Figure 9 :

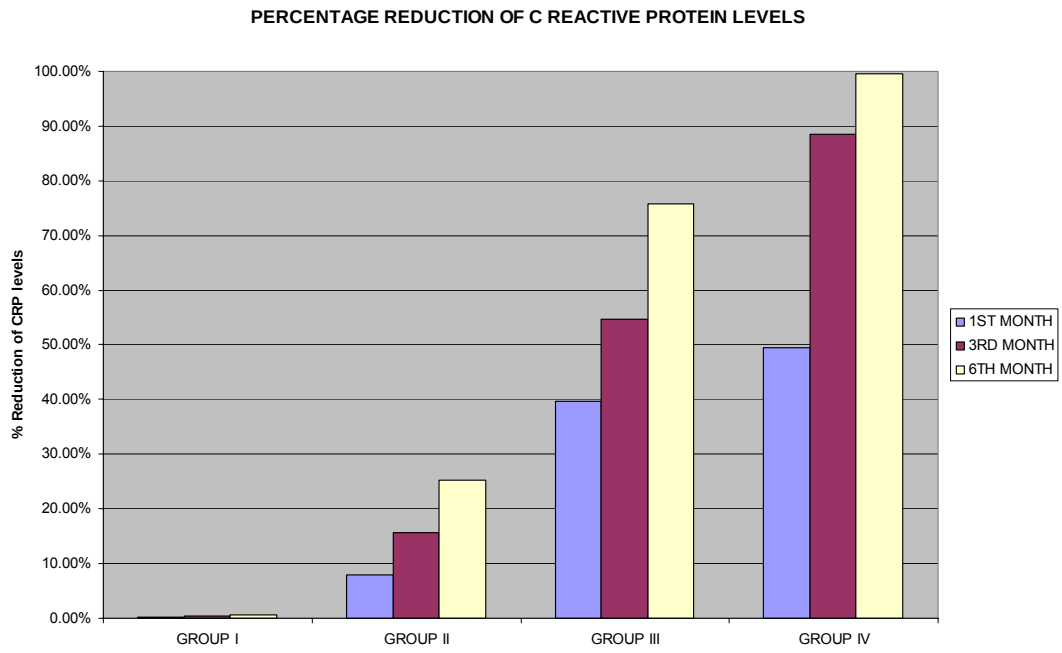


Table 9 :

Shows the percentage reduction of C reactive protein levels from baseline, at the end of 1st month, 3rd month and 6th month among the study groups

Figure 9 :

Shows the schematic representation of percentage reduction of C reactive protein levels from baseline, at the end of 1st month, 3rd month and 6th month among the study groups

COMPARISON OF CHANGE OF HEMOGLOBIN CONCENTRATION AMONG GROUPS

Table 10 :

Parameters	Group								Significance
	GROUP I		GROUP II		GROUP III		GROUP IV		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Hb_base Line	11.23	1.40	11.21	1.17	11.30	1.05	11.30	1.07	F=0.04 P=0.99(NS)
Hb_1st month	11.18	1.32	11.23	1.24	11.32	1.00	11.43	1.21	F=0.23 P=0.88(NS)
Hb_3rd month	11.06	1.15	11.15	1.16	11.39	0.95	11.24	1.00	F=0.46 P=0.71(NS)
Hb_6th month	10.94	1.03	11.40	1.22	11.41	0.91	11.49	1.00	F=1.57 P=0.20(NS)
Significance	F=0.30 P=0.82 (NS)		F=0.22 P=0.82 (NS)		F=0.08 P=0.97 (NS)		F=0.29 P=0.82 (NS)		

Figure10 :

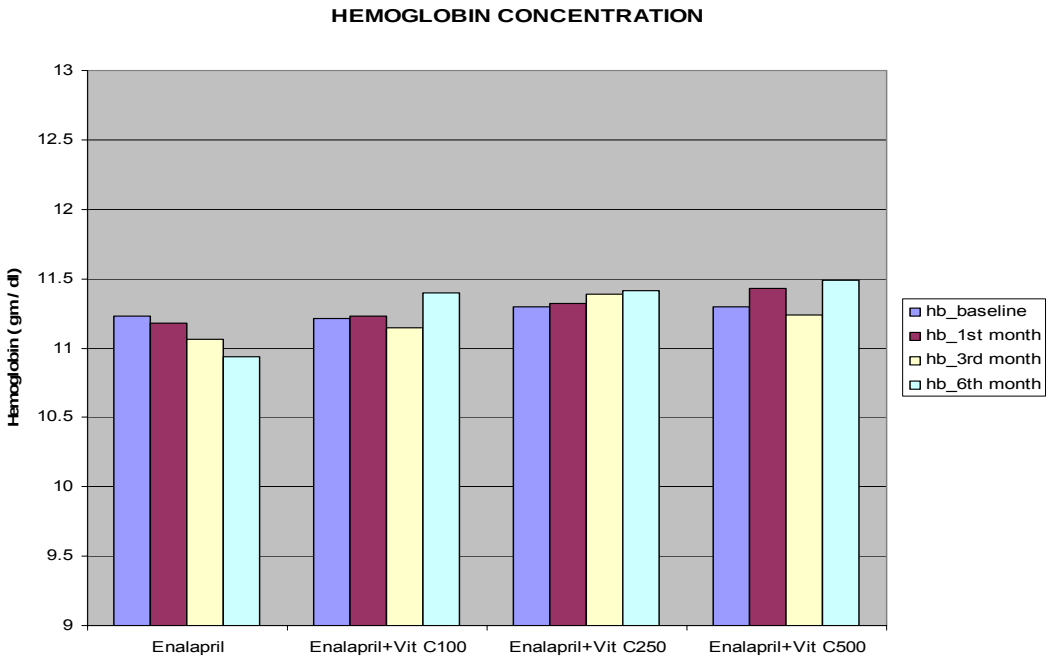


Table 10 shows the mean HEMOGLOBIN LEVELS in each group at baseline, at the end of 1st month, 3rd month and 6th month.

At the baseline

There was no statistical significant difference among groups at baseline.

At the end of 1st month

There was no statistical significant difference among groups at the end of 1st month

At the end of 3rd month

There is no statistical significant difference among groups at the end of 3rd month

At the end of 6th month

There is no statistical significant difference among groups at the end of 6th month

Figure 10 : shows the diagrammatic representation of the mean Hemoglobin concentration in all the study groups at base line, at the end of 1st month, 3rd month and 6th month.

COMPARISON OF BLOOD SUGAR CHANGES BETWEEN THE STUDY GROUPS

Table 11:

Parameters	Group								Significance
	GROUP I		GROUP II		GROUP III		GROUP IV		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
BS_base Line	95.61	15.83	98.85	13.48	90.86	13.92	97.22	13.34	F=1.63 P=0.19(NS)
BS_1st month	96.07	12.45	97.07	13.31	91.64	12.33	97.30	10.74	F=1.28 P=0.28(NS)
BS_3rd month	93.86	9.71	97.59	9.49	92.36	11.33	96.96	8.86	F=1.75 P=0.18(NS)
BS_6th month	96.61	9.20	98.93	9.20	94.64	11.39	95.93	9.74	F=0.89 P=0.44(NS)
Significance	F=0.27 P=0.85NS)		F=0.17 P=0.91NS)		F=0.49 P=0.69(NS)		F=0.09 P=0.96(NS)		

Figure 11 :

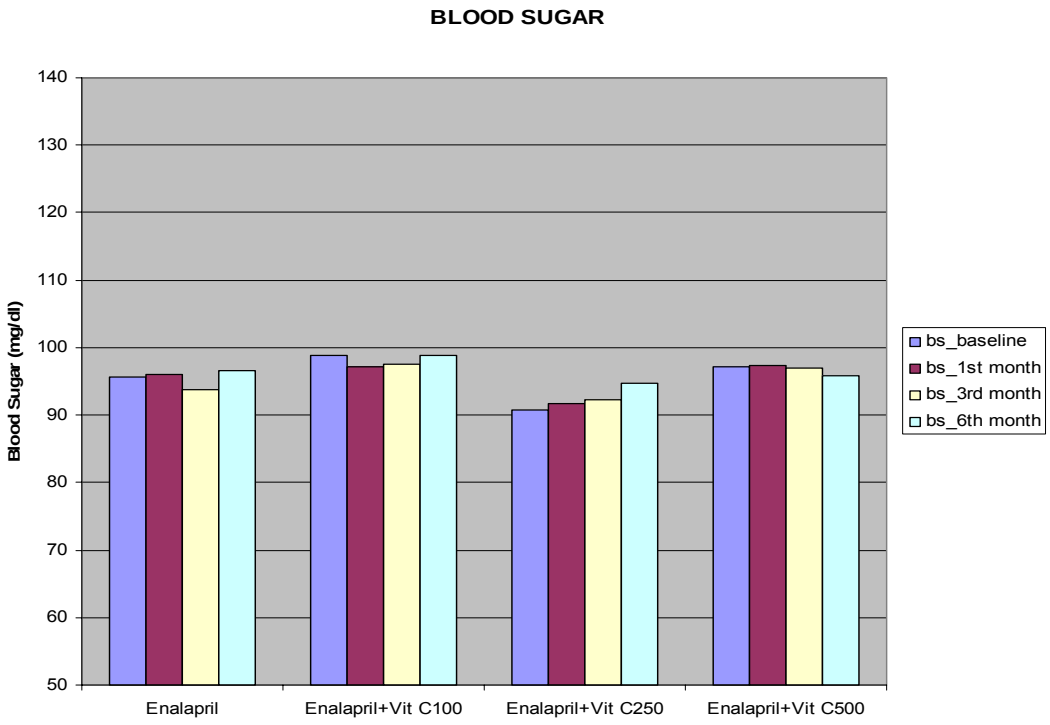


Table 11 shows the mean BLOOD SUGAR LEVELS in each group at baseline, at the end of 1st month, 3rd month and 6th month.

At the baseline

There was no statistical significant difference among groups at baseline.

At the end of 1st month

There was no statistical significant difference among groups at the end of 1st month

At the end of 3rd month

There is no statistical significant difference among groups at the end of 3rd month

At the end of 6th month

There is no statistical significant difference among groups at the end of 6th month

Figure 11 shows the diagrammatic representation of the mean Blood Sugar levels in all the study groups at base line, at the end of 1st month, 3rd month and 6th month.

COMPARISON OF BLOOD UREA CONCENTRATION AMONG TREATMENT GROUPS

Table 12 :

Parameters	Groups								Significance
	GROUP I		GROUP II		GROUP III		GROUP IV		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Urea_base Line	26.36	7.18	26.67	5.01	28.07	7.49	28.30	6.28	F=0.61 P=0.61(NS)
Urea_1st month	26.64	6.81	27.07	4.85	27.50	5.69	27.81	5.19	F=0.22 P=0.88(NS)
Urea_3rd month	26.89	6.54	28.15	4.93	27.93	5.35	28.63	4.84	F=0.49 P=0.68(NS)
Urea_6th month	27.29	6.05	26.96	4.87	28.36	5.35	29.30	4.96	F=1.08 P=0.36(NS)
Significance	F=0.09 P=0.96 (NS)		F=0.46 P=0.71 (NS)		F=0.09 P=0.96 (NS)		F=0.37 P=0.77 (NS)		

Figure 12 :

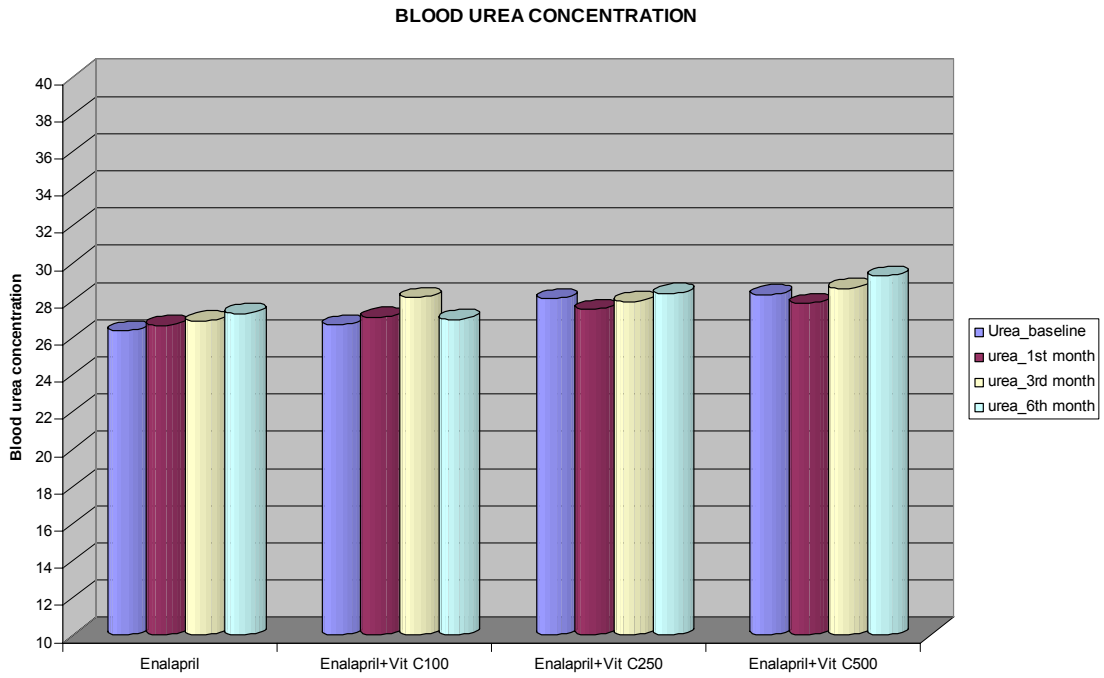


Table 12 shows the mena Blood Urea levels in each group at

baseline, at the end of 1st month, 3rd month and 6th month.

At the baseline

There was no statistical significant difference among groups at baseline.

At the end of 1st month

There was no statistical significant difference among groups at the end of 1st month

At the end of 3rd month

There is no statistical significant difference among groups at the end of 3rd month

At the end of 6th month

There is no statistical significant difference among groups at the end of 6th month

Figure 12 shows the diagrammatic representation of the mean Blood Urea levels in all the study groups at base line, at the end of 1st month, 3rd month and 6th month.

COMPARSION OF SERUM CREATININE LEVELS AMONG TREATMENT GROUPS

Table 13 :

Parameters	Group								Significance
	GROUP I		GROUP II		GROUP III		GROUP IV		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Cre_base Line	0.80	0.13	0.83	0.15	0.84	0.14	0.83	0.15	F=0.43 P=0.73(NS)
Cre_1st month	0.80	0.12	0.80	0.12	0.77	0.11	0.79	0.11	F=0.36 P=0.78(NS)
Cre_3rd month	0.77	0.11	0.76	0.12	0.78	0.13	0.78	0.08	F=0.22 P=0.88(NS)
Cre_6th month	0.81	0.11	0.79	0.11	0.76	0.11	0.78	0.10	F=0.93 P=0.43(NS)
Significance	F=0.55 P=0.65(NS)		F=1.445 P=0.23(NS)		F=1.95 P=0.13(NS)		F=1.11 P=0.35(NS)		

Figure 13 :

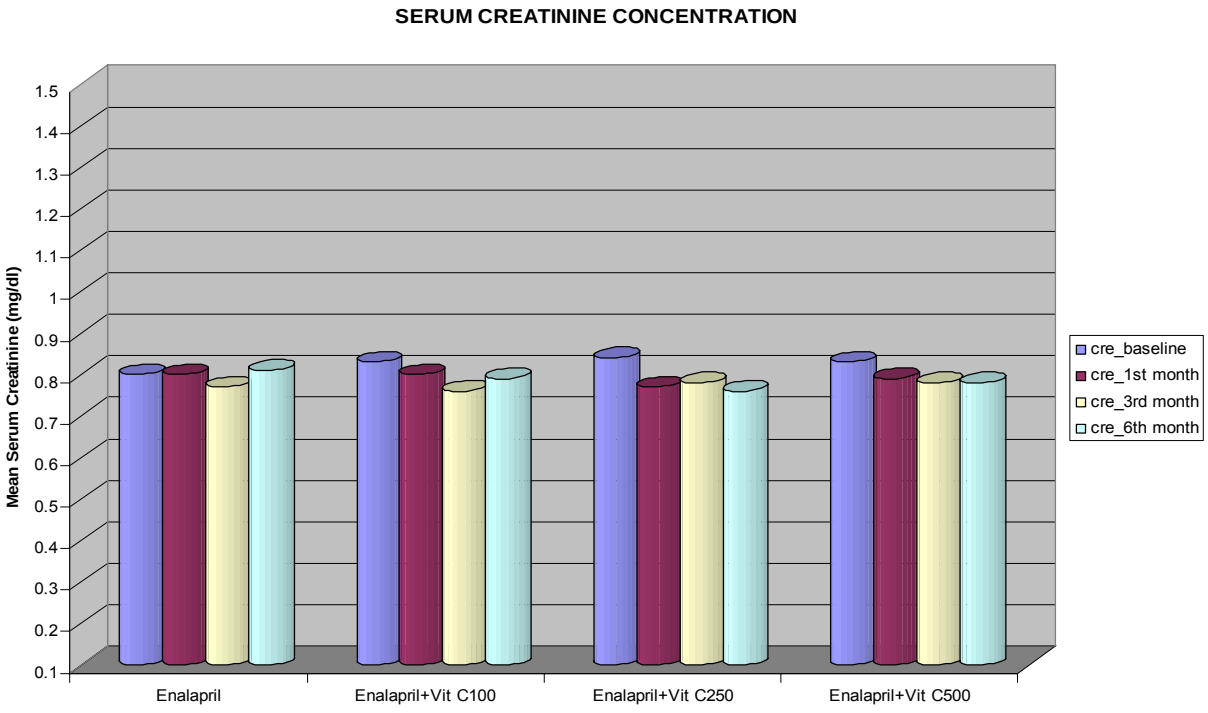


Table 13 shows the mean Serum Creatinine levels in each group at baseline, at the end of 1st month, 3rd month and 6th month.

At the baseline

There was no statistical significant difference among groups at baseline.

At the end of 1st month

There was no statistical significant difference among groups at the end of 1st month

At the end of 3rd month

There is no statistical significant difference among groups at the end of 3rd month

At the end of 6th month

There is no statistical significant difference among groups at the end of 6th month

Figure 13 shows the diagrammatic representation of the mean Serum Creatinine levels in all the study groups at base line, at the end of 1st month, 3rd month and 6th month.

COMPARISON OF CHANGES OF SGOT LEVELS AMONG TREATMENT GROUPS

Table 14 :

Parameters	Group								Significance
	GROUP I		GROUP II		GROUP III		GROUP IV		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
SGOT_base Line	19.82	2.98	20.52	2.83	20.11	2.88	19.89	2.22	F=0.35 P=0.79(NS)
SGOT_1st month	20.46	2.73	20.74	3.53	20.25	3.31	20.11	3.31	F=0.19 P=0.89(NS)
sgot_3rd month	20.50	3.50	20.33	2.91	20.54	2.06	20.30	2.85	F=0.05 P=0.99(NS)
SGOT_6th month	19.89	3.34	20.85	3.44	19.61	2.99	20.00	2.96	F=0.77 P=0.55(NS)
Significance	F=0.37 P=0.78(NS)		F=0.14 P=0.92(NS)		F=0.52 P=0.67(NS)		F=0.09 P=0.96(NS)		

Figure 14 :

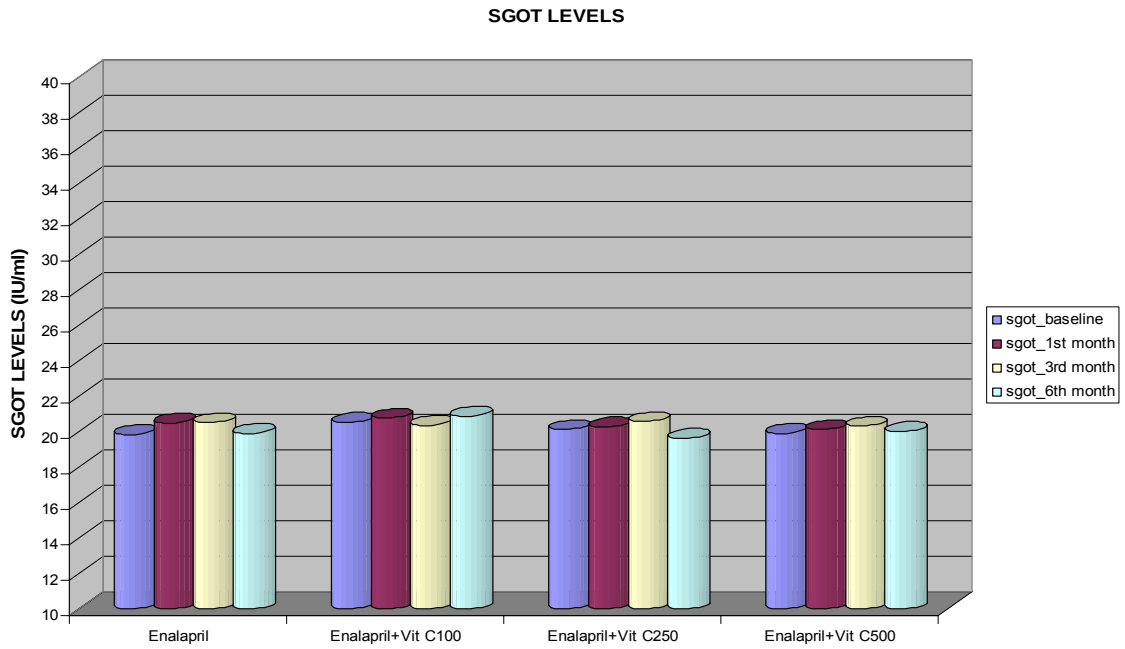


Table 14 shows the mean AST (SGOT) levels in each group at baseline, at the end of 1st month, 3rd month and 6th month.

At the baseline

There was no statistical significant difference among groups at baseline.

At the end of 1st month

There was no statistical significant difference among groups at the end of 1st month

At the end of 3rd month

There is no statistical significant difference among groups at the end of 3rd month

At the end of 6th month

There is no statistical significant difference among groups at the end of 6th month

Figure 14 shows the diagrammatic representation of the mean AST (SGOT) levels in all the study groups at base line, at the end of 1st month, at the end of 3rd and 6th month.

COMPARISON OF CHANGES OF SGPT LEVELS AMONG THE TREATMENT GROUPS

Table 15 :

Parameters	Group								Significance
	GROUP I		GROUP II		GROUP III		GROUP IV		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
SGPT_base Line	**20.46**	**2.77**	**20.48**	**2.10**	**20.07**	**2.83**	**20.37**	**2.75**	F=0.14 P=0.93(NS)
SGPT_1st month	**21.25**	**3.92**	**19.96**	**3.02**	**20.32**	**2.72**	**20.37**	**2.99**	F=0.81 P=0.48(NS)
SGPT_3rd month	**21.71**	**4.06**	**20.48**	**3.33**	**19.57**	**3.34**	**20.93**	**3.16**	F=1.83 P=0.15(NS)
SGPT_6th month	**21.54**	**3.92**	**19.48**	**3.14**	**20.18**	**2.21**	**20.70**	**3.57**	F=1.93 P=0.12(NS)
Significane	F=0.62 P=0.60(NS)		F=0.72 P=0.54(NS)		F=0.38 P=0.67NS)		F=0.20 P=0.89(NS)		

Figure 15 :

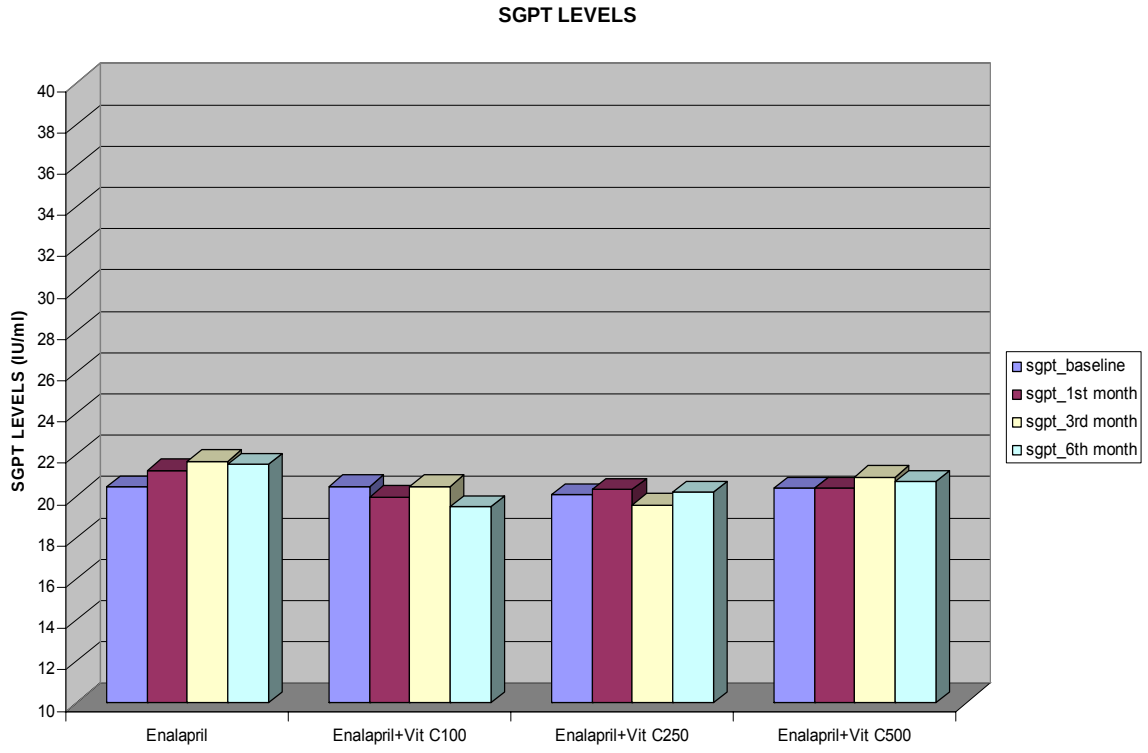


Table 15 shows the mean ALT (SGPT) levels in each group at

baseline, at the end of 1st month, at the end of 3rd month and 6th month.

At the baseline

There was no statistical significant difference among groups at baseline.

At the end of 1st month :

There was no statistical significant difference among groups at the end of 1st month

At the end of 3rd month

There is no statistical significant difference among groups at the end of 3rd month

At the end of 6th month

There is no statistical significant difference among groups at the end of 6th month

Figure 15 the diagrammatic representation of the mean ALT (SGPT) levels in all the study groups at base line, at the end of 1st month, 3rd month and 6th month.

COMPARISON OF ADVERSE EFFECTS AMONG THE GROUPS

Table 16 :

Sl No	Side effects	GROUP I	GROUP II	GROUP III	GROUP IV	Chi square Test χ^2	P value
1	**Nausea**	1	1	1	2	0.70	0.87
2	**Vomiting**	0	0	1	1	2.40	0.56
3	**Dyspepsia**	0	0	0	1	3.10	0.38
4	**Diarrhoea**	0	0	0	1	3.10	0.38
5	**Dizziness**	2	1	1	2	0.71	0.87
6	**Headache**	1	0	1	1	1.00	0.8
7	**Cough**	2	2	2	1	0.43	0.93
8	**Fatigue**	2	2	2	1	0.43	0.93
9	**Total**	8	6	8	10	1.45	0.69

Table 17 :

SL NO	GROUPS	ADVERSE EFFECTS		TOTAL	CHI SQUARE TEST
		PRESENT	ABSENT		
1	GROUP I	8	20	28	$\chi^2 = 1.45$ P = 0.69
2	GROUP II	6	21	27	
3	GROUP III	8	20	28	
4	GROUP IV	10	17	27	

Table 16 :

Shows the occurrence of various adverse effects among the treatment groups and their statistical significance.

Table 17 :

Shows the Adverse effects among the study groups. Data was analyzed using Chi-Square test and found there was no statistical significance (P=0.69) among the groups in the occurrence of adverse effects.

Figure 16 :

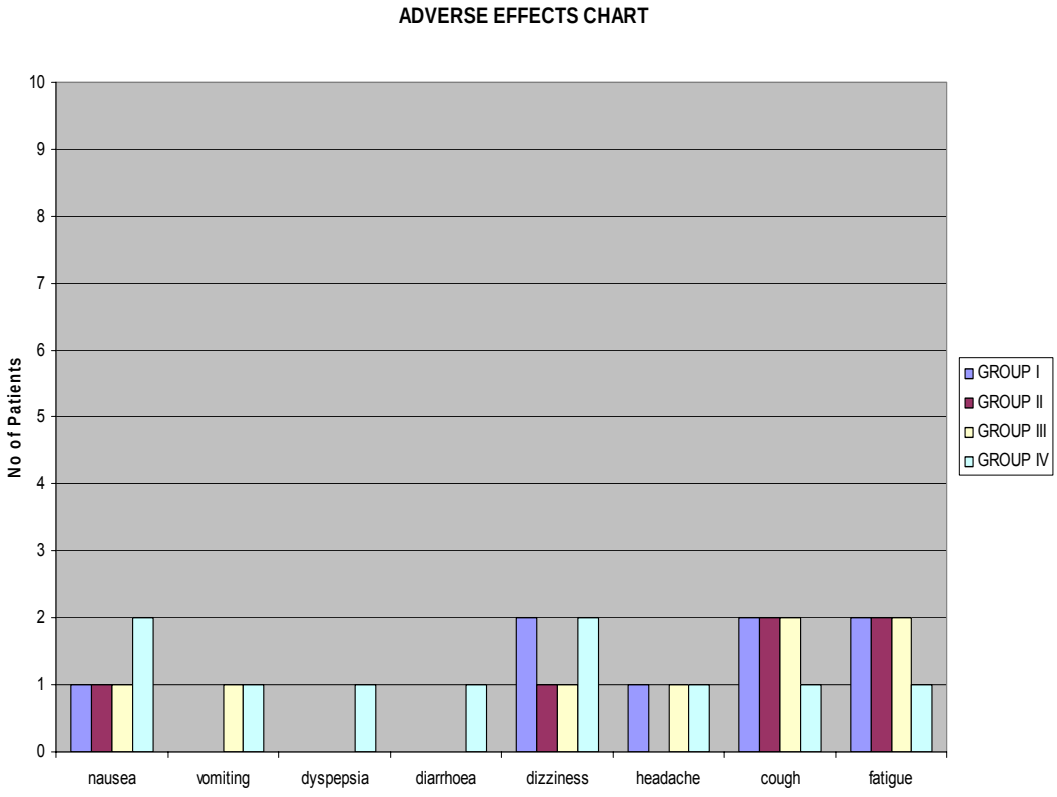

ADVERSE EFFECTS CHART
No of Patients
10
9
8
7
6
5
4
3
2
1
0
nausea
vomiting
dyspepsia
diarrhoea
dizziness
headache
cough
fatigue
GROUP I
GROUP II
GROUP III
GROUP IV

Figure 16 :

Shows the diagrammatic representation of occurrence of various adverse effects among the treatment groups.

DISCUSSION

DISCUSSION

Hypertension , one of the leading cause of morbidity and mortality in both developing and developed countries. Hypertension when untreated, leads to various cardiovascular risks such as increased incidence of atherosclerosis, coronary artery disease and cerebrovascular risks such as stroke. It has been found that increased levels of C reactive protein have been associated with increased incidence of stroke and other cardiovascular risks.

It has been found that increased levels of C reactive protein in hypertensive patients decreases the elasticity of large arteries and increase the arterial stiffness. Hypertension, being an oxidative stress, there will be degradation of nitric oxide which is a potent endogenous vasodilator. The subsequent reduction of nitric oxide levels in hypertensive patients results in increased responsiveness to vasoconstrictor amines such as catecholamines which increases the blood pressure.

None of the anti-hypertensive drugs reduces the C reactive protein levels, which not only increases the arterial stiffness but also increases the risk of cardiovascular complications such as coronary artery disease and increased incidence of cerebrovascular accidents such as stroke.

Studies suggest that Vitamin C, a potent anti-oxidant by scavenging free radicals, prevents the degradation of nitric oxide decreases the constrictor response of catecholamines and aids in the reduction of blood pressure. Vitamin C in addition reduces the levels of C reactive protein which found to decrease the elasticity of larger arteries and increasing arterial

stiffness. Vitamin C by reducing C reactive protein levels helps in decreasing the blood pressure in hypertensive patients and prevents its complications.

Hence the study was undertaken to find out the efficacy and tolerability of Vitamin C as add on therapy to standard anti-hypertensive therapy in the reduction of blood pressure and C reactive protein levels in hypertensive patients.

The study was conducted in the Outpatient Department of Hypertension Clinic, Department of Internal Medicine, Madras Medical College and Government General Hospital, Chennai.

Out of 529 patients screened, 120 patients who fulfilled the inclusion and exclusion criteria were recruited for the study. They were randomized into four groups, Group I, Group II, Group III and Group IV, each group consisting of 30 patients. Group I received Enalapril 5 mg BD, Group II received Enalapril 5 mg BD with Vitamin C 100 mg OD, Group III received Enalapril 5 mg BD with Vitamin C 250 mg OD and Group D received Enalapril 5 mg BD with Vitamin C 500 mg OD for a period of 6 months.

Efficacy variables such as Systolic blood pressure, Diastolic blood pressure and C reactive protein levels were measured at the baseline, at the end of 1st month, at the end of 3rd month and at the end of 6th month of the study. Other hematological investigations such as complete hemogram, blood sugar, blood urea, serum creatinine, Liver function tests such as SGOT, SGPT, serum alkaline phosphatase, total bilirubin, total protein, albumin were done at the baseline, at the end of 1st month, at the end of 3rd month and 6th month of the study.

Regarding demographic characteristics, parameters such as age distribution, body mass index and sex distribution were taken into account and analyzed for any statistical significance. There is no statistical significane among the study groups in demographic characteristics.

In this study, Vitamin C at the dose of 100 mg and 250 mg when added with Enalapril produces significant decrease in systolic blood pressure at the end of 1st month , 3rd month and 6th month.

Vitamin C at the dose of 500 mg when added with Enalapril 5 mg BD causes statistical significant reduction of systolic blood pressure of 11.15% at the end of 1st month, reduction of 18.29% at the end of 3rd month and 24.73% at the end of 6th month of the study. Enalapril 5 mg BD alone group produces reduction of systolic blood pressure of 3.45% at the end of 1st month, 7.17% at the end of 3rd month and 12.64% at the end of 6th month of the study.

One study comparing 500 mg/day of vitamin C supplement 1 month, showed a significant decrease in systolic BP of 9.9 mm Hg[74]. Another study showed that Vitamin C 500mg once daily produced fall of blood pressure by 9% after 4 weeks of study.[75, 76,77,78]

In this study, Vitamin C at the dose of 500 mg when added with Enalapril 5 mg BD causes statistical significant reduction of diastolic blood pressure of 12.72% at the end of 3rd month and 15.73% at the end of 6th month of the study. Enalapril 5 mg BD alone group produces reduction of diastolic blood pressure of 7.08% at the end of 3rd month and 10.07% at the end of 6th month of the study.

In our study, it has been found even though Group III showed significant reduction of C reactive protein levels, only patients in Group IV

(Vitamin C 500 mg) showed reduction of C reactive protein to the desirable level (<1mg/dl).

In our study, it has been found that Vitamin C at the dose of 500 mg once daily when given along with Enalapril 5mg BD causes reduction of C reactive protein levels to 49.47% at the end of 1st month, 88.54% at the end of 3rd month and 99.64% at the end of 6th month when compared to Enalapril 5mg OD alone group in which the reduction of C reactive protein level was 0.27% at the end of 1st month, 0.36% at the end of 3rd month and 0.54% at the end of 6th month of the study. One study showed that ingestion of Vitamin C 250 mg / day and 500 mg / day showed significant reduction of C reactive protein levels at the end of 2 months[79.]

Hence, it has been found even though Vitamin C 100mg and 250 mg Group showed reduction of systolic and diastolic blood pressure, only patients in Group III (Vitamin C 500 mg) showed reduction of C reactive protein to desirable levels.

Other hematological and biochemical parameters were measured at the baseline, at the end of 1st month, at the end of 3rd month and the end of 6th month and found to have no statistical difference among the study groups.

Mild adverse effects such as nausea, vomiting , dyspepsia, diarrhea, dizziness, headache, cough and fatigue occurred among study groups which does not show any statistical significant difference (P=0.69) among the groups and all the adverse effects subsided without any medications.

Hence, Vitamin C at the dose of 500 mg / day produces significant reduction of systolic and diastolic blood pressure with reduction of C reactive protein levels to the desirable levels.

CONCLUSION

CONCLUSION :

From our study, we conclude that

- Vitamin C at the dose of 500 mg OD as an add on therapy to Enalapril 5mg BD causes significant reduction of both systolic and diastolic blood pressure.
- Vitamin C 500mg also significantly decreases the C reactive protein to desirable levels.
- Vitamin C 500mg OD supplementation to the standard anti-hypertensive drugs may produce better reduction of blood pressure and C reactive protein levels.
- Vitamin C 500 mg may be recommended as an adjuvant to regular anti-hypertensive regimen to reduce cardiovascular and cerebrovascular risks associated with hypertension.

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BIBILOGRAPHY

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APPENDICES

Appendix 1

ABBREVATIONS

- AA : Ascorbic acid
- ACE : Angiotensin converting enzyme
- ADH : Anti diuretic hormone
- ALT : Aspartate aminotransferase
- ARBs : Angiotensin receptor blockers
- ASD : Autism spectrum disorder
- AST : Aspartate aminotransferase
- BMI : Body mass index
- BS : Blood sugar
- CD : Collecting duct
- Cre : Creatinine
- CRP : C-reactive protein
- CVAs : Cerebrovascular accidents
- CVD : Cardiovascular disease
- DBP : Diastolic blood pressure
- DCT : Distal convoluted tubule
- dl : Deciliter
- ELISA : Enzyme linked immunosorbent assay
- Hb : Hemoglobin
- HDL : High density lipoprotein
- HT : Hypertension

- ICAM-1 : Intercellular adhesion molecule
- IL-6 : Interleukin 6
- JAMA : The Journal of the American Medical Association
- Kg : Kilogram
- LDL : Low density lipoprotein
- MCP-1 : Monocyte chemoattractant protein
- Mg : Milligram
- MI : Myocardial infarction
- Mm Hg : Millimeter of mercury
- MR : Mineralocorticoid receptor
- RA : Rheumatoid arthritis
- RTI : Respiratory tract infection
- SAP : Serum alkaline phosphatase
- SBP : Systolic blood pressure
- SGOT : Serum glutamic oxaloacetic transaminase
- SGPT : Serumglutamic pyruvic transaminase
- TNF-α : Tumor necrosis factor α
- TPR : Total peripheral resistance
- Vit : Vitamin

Appendix 2

Case Record Form

Efficacy and tolerability of Vitamin C as an add on therapy to the standard anti-hypertensive regimen in the reduction of blood pressure and C reactive protein levels in hypertensive patients

Name :

Age :

Sex :

O.P. No :

Group :

Randomization No :

Address :

Examination

a. General Examination

Weight Height BMI

Pallor Jaundice Odema Others

Nutritional status

b. CVS Examination : Pulse BP

c. RS Examination :

d. Abdomen Examination

e. CNS Examination :

Investigations :

SL.NO	PARAMETERS	BASELINE	1ST MONTH	3RD MONTH	6TH MONTH
1	C reactive protein				
2	Blood sugar				
3	Blood urea				
4	Serum Creatinine				
5	Hemoglobin				
6	Total count				
7	Differential count				
8	SGOT				
9	SGPT				
10	SAP				
11	Total bilirubin				
12	Total protein				
13	Serum albumin				

Adverse Effects :

Concomitant Medications :

Others :

Tamil consent form *Appendix 3*

MŒî x¥òjš got«

MŒÉ‹ jiy¥ò

“ïu¤j mG¤j nehahËfS¡fhd eilKiw kh¤âiuíl‹ it£Ä‹ á v‹D« kUªâ‹ âw‹, ghJfh¥ò¤j‹ik, ïu¤j mG¤j« k‰W«
á-Çah¡o› òuj¤â‹ Fiwjš g‰¿a x® kU¤Jt MŒî”

bga®_____ òw nehahË v©. _____
KftÇ_____ MŒî nr®¡if v©. _____
_____ taJ _____
_____ ghÈd« ( ) M© ( ) bg©

eh‹ _____taJ _____ v‹Dila RaÃidîl‹ k‰W« KG Rjªâu¤Jl‹ ïªj kU¤Jt MŒÉš v‹id nr®¤J¡ bfhŸs r«kâ¡»nw‹.
MŒÉ‹ jiy¥ò

“ïu¤j mG¤j nehahËfS¡fhd eilKiw kh¤âiuíl‹ it£Ä‹ á v‹D« kUªâ‹ âw‹, ghJfh¥ò¤j‹ik, ïu¤j mG¤j« k‰W«
á-Çah¡o› òuj¤â‹ Fiwjš g‰¿a x® kU¤Jt MŒî”
vd¡F És¡f¥g£l Ñœ¡f©l Éõa§fS¡F eh‹ vdJ r«kj¤ij jU»nw‹.

- ïªj MŒÉ‹ neh¡f«, kU¤Jt KiwfŸ, gÇnrhjid KiwfŸ, vd¡F âU¥âíW« tifÆš És¡f¥g£ld.
- gÇnrhjid brŒtj‰fhf v‹ clÈÈUªJ ïu¤j« k‰W« áWÚ® vL¡f¥gl nt©oíŸsjhf m¿»nw‹.
- eh‹ vL¤J tU»‹w k‰W« K‹ c£bfh©l kUªJfŸ g‰¿a Étu§fis MŒthsÇl« m¿É¡f r«kj«. ïªj g§nf‰wÈ‹ ã‹ò mtÇ‹ mDkâÆ‹¿ eh‹ vªj kUªJ« c£bfhŸs kh£nl‹ v‹W« bjÇÉ¡»nw‹.
- vd¡F« k‰W« kUªJ MœthsU¡F«, ïªj MŒÉÈUªJ vªj xU ÃiyÆY« ÉyFtj‰nfh mšyJ Éy¡Ftj‰nfh KG cÇik ïU¥gjhf m¿»nw‹.
- v‹Dila kU¤Jt¡ F¿¥ngLfis ïªj MŒÉš ga‹gL¤â¡ bfhŸs r«kâ¡»nw‹. MŒî ikaK«, MœthsU« v‹Dila bga® k‰W« áy Étu§fis ïufáakhf it¥gjhf m¿»nw‹.

_____ nehahËÆ‹ bga®	_____ ifbaG¤J	_____ njâ
_____ rh£áÆ‹ bga®	_____ ifbaG¤J	_____ njâ
_____ MŒthsÇ‹ bga®	_____ ifbaG¤J	_____ njâ

Appendix 4

PATIENT CONSENT FORM

"EFFICACY AND TOLERABILITY OF VITAMIN C AS AN ADD ON THERAPY TO THE STANDARD ANTI-HYPERTENSIVE REGIMEN IN THE REDUCTION OF BLOOD PRESSURE AND C REACTIVE PROTEIN LEVELS IN HYPERTENSIVE PATIENTS"

Study Centre : Dept of Internal Medicine, Govt.General Hospital,Chennai.
Patient's Name : _____
Patinet's Age : _____
Identification Number : _____

Patients may check (✓) these Boxes

I confirm that i have understood the purpose and procedure for the above study. I have the opportunity to ask the question and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving any reason, without my legal rights being affected. ☐

I understand that the investigator of the clinicl study, the ethics committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I agree to this access. However, I understand that my identify will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and to faithfully co-operate with the study team, and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

I hereby agree to allow the investigator to take blood from me for the laboratory investigations until the completion of study.. ☐

I hereby give permission to undergo complete physical examination, and diagnostic tests including hematological, Biochemical, Radiological and urine examination. ☐

Signature / Thumb Impression _____ Place _____ Date of the patient.
Patient's Name&Address : _____
_____
Signature of the Investigator : _____ Place _____ Date
Study Investigator's Name : _____